DISCUSSÃO

No presente trabalho, realizou-se o bloqueio da fosfodiesterase pelo citrato de sildenafil em ratas com a bexiga desnervada. os resultados mostraram que os picos pressóricos vesicais máximos e minimos para micção não variam nas ratas normais e nem naquelas desnervadas, ocorrendo variação significante após a infusão gástrica do citrato de sildenafil. Observou-se queda significante das pressões máximas e mínimas quando se compara as ratas normais com as desnervadas sem e com citrato de sildenafil. A comparação entre as pressões máximas das bexigas desnervadas e com o citrato de sildenafil mostrou que não há nível de significância, mas quando se compara as pressões mínimas observa-se que houve queda significante. A interpretação do modelo experimental mostra que após a desnervação a bexiga se comporta como um reservatório elástico[8], cuja pressão interna depende do fluxo de vazão, uma vez que o fluxo de infusão vesical é contínuo. Essa pressão é proporcional à resistência da uretra ($R= P/ Q^2$)[6], que por sua vez traduz a pressão de fechamento uretral. Assim, as pressões vesicais das bexigas desnervadas e com o citrato de sildenafil expressam as pressões de fechamento da uretra nas condições do experimento. É interessante a observação de que as pressões máximas das bexigas desnervadas sem e com o citrato de sildenafil são semelhantes , mas diferem em relação às pressões mínimas. Esse fato pode espelhar o que ocorre com o corpo cavernoso em que há necessidade do estímulo inicial para que ocorra a ação relaxadora da droga. Esses achados necessitam de estudos mais profundos para sob o ponto de vista farmacológico verificar se essa droga terá aplicação clínica em situações que haja necessidade de diminuição da pressão mínima da uretra.

CONCLUSÕES

1) A desnervação vesical promove queda nas pressões uretrais máxima e mínima;
2) O citrato de sildenafil amplia a faixa pressórica de trabalho da uretra devido a diminuição da pressão mínima;
3) O citrato de sildenafil não altera a pressão uretral máxima depois da desnervação.

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ABSTRACT – Background: Nitric oxide acts as a non-adrenergic and non-cholinergic neurotransmitter in the bladder and urethra. It activates the guanilatocyclase that transforms GMP in cGMP which promotes muscle relaxation. Sildenafil citrate increases the cGMP concentration by inhibiting the phosphodiesterase responsible for its hydrolysis. **Methods:** 6 female rats weighing 200g were anesthetized with urethane at a dosage of 1.25mg/kg. All animals underwent cystostomy with a catheter P50 connected by a Y to an infusion pump and to a polygraph Narco-Biosystem. The cystometry was performed trice in each animal: right after the cystostomy, after surgical of bladder denervation and 1h after gastric infusion of 1mg/kg of sildenafil citrate. Maximum (MaP) and minimum (MiP) vesical pressure were compared in the following moments: I – before bladder denervation, II – after bladder denervation and III – after bladder denervation and sildenafil administration. Wilcoxon test was used for a level of significance of 5%. **Results:** Mean values of MaP were: I – 86.6±10.1, II – 42.6±15.0 and III – 30.8±12.4. The corresponding values of MiP were: : I – 72.1±18.9, II – 31.1±9.8 and III – 14.5±9.5. The comparison between MaP and MiP in each moment showed difference only in moment III ($p<0.01$). For MaP p value was <0.002 in IxII and IxIII and >0.05 in IIxIII. For MiP the p values were <0.004 in IxII, <0.002 in IxIII and <0.01 in IIxIII. **Conclusion:** 1) Bladder denervation reduces maximum and minimum urethral pressure; 2) Sildenafil citrate reduces the minimum urethral pressure widening the interval between the peak and bottom pressures; and, 3) Sildenafil citrate does not interfere on the peak urethral pressure after bladder denervation.

KEY WORDS: Sildenafil citrate. Denervation. Urethra. Bladder. Urodynamics.

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11 – ARTIGO ORIGINAL

Reactive oxygen species inactivation improves pancreatic capillary blood flow in caerulein-induced pancreatitis in rats

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ABSTRACT- Purpose: Reactive oxygen species (ROS) inactivation was studied to determine alterations in the pancreatic capillary blood flow (PCBF) during caerulein-induced pancreatitis in rats. **Methods:** A laser-Doppler flowmeter to measure PCBF and N-t-Butyl-Phenylnitrone (PBN) compound to inactivate ROS were used. Forty rats were divided in groups: 1) control; 2) caerulein; 3) PBN; 4) caerulein+PBN. Serum biochemistry and histopathological analyses were performed. **Results:** PCBF measured a mean of 109.08 ± 14.54%, 68.24 ± 10.47%, 102.18 ± 10.23% and 87.73 ± 18.72% in groups 1, 2, 3 and 4, respectively. PCBF in groups 2 and 4 decreased 31.75 ± 16.79% and 12.26 ± 15.24%, respectively. Serum amylase was 1323.70 ± 239.10 U/l, 2184.60 ± 700.46 U/l, 1379.80 ± 265.72 U/l and 1622.10 ± 314.60 U/l in groups 1, 2, 3 and 4, respectively. There was a significant difference in the PCBF and serum amylase when compared groups 2 and 4. Cytoplasmatic vacuolation was present in groups 2 and 4. Otherwise, no qualitative changes were seen. **Conclusion:** ROS inactivation improves PCBF and minimizes the serum amylase increase during caerulein-induced pancreatitis. ROS effect may be one of the leading causative events in this model of acute pancreatitis.

KEY WORDS: Blood flow. Caerulein. Laser-Doppler. Oxygen radicals. Pancreatitis. Spin-trapping nitrone.

INTRODUCTION

The pathogenesis of septic shock, adult respiratory distress syndrome, acute renal failure, and participation in the ischemia-reperfusion organs like myocardial infarction, stroke, and organ transplantation seem to be involved with the production of reactive oxygen species (ROS)[1,2,3]. The increase in capillary permeability and vascular reactivity has been attributed to ROS generation[4]. The generation of ROS appears to play a central role in the pathogenesis[5] of ischemic, alcoholic and gallstone pancreatitis animal models. In the caerulein-induced pancreatitis model, formation of ROS has also been reported [6].

Recently the N-tert-phenyl-buthyl-nitrone (PBN), a spin-trapping nitrone, has been used to determine the presence of ROS[7]. The ROS effects can be analyzed when spin-trapping nitrone is employed once the nitrone compound reacts covalently with ROS creating a relatively stable radical [8].

The purpose of this experiment was to study pancreatic capillary blood flow (PCBF) changes, using a laser-Doppler flowmeter, to determine whether ROS inactivation by a spin-trapping nitrone (PBN) changes the PCBF during caerulein-induced pancreatitis.

METHODS

Surgical preparation: Forty Sprague-Dawley male rats weighing between 290 and 448 g were used. All rats were starved for 18 hours prior to the experiment, except for water *ad libitum.* A single subcutaneous injection of 25% urethan anesthetic (1.75 g of urethane/ 1000 g body weight; Urethane, Sigma, St. Louis, MO) was used. The body temperature during the experiment was kept between 36.4 -36.6 C using a thermo controller (made by Béla Kurucz, E.E., Maglód, Hungary). An arterial and venous line was obtained via the right iliac artery and left iliac vein that were isolated and cannulated with heparinized PE-50 polyethylene tubing. The abdominal wall was opened by a mid-line incision extending from the xiphoid to the suprapubic region. The pancreas was isolated and two gauze sponges were placed between the posterior abdominal wall and the pancreas. The laser-Doppler probe was placed on the anterior surface of the body of the pancreas.

Measurement of PCBF, Blood pressure (BP) and heart rate (HR): PCBF

measurement was performed with a laser-Doppler Capillary Perfusion Monitor (model LD- 6000, Medpacific Corp., Seattle, W A)[9]. The laser-Doppler flowmeter was connected to a computer (IBM PS/2 model 50Z, Armonk, NY) equipped with an appropriate software package (LD-6000 Data Collection; written by Howard Amols, Ph.D., Columbia University, New York, NY) that collected, recorded and stored six data points per second of PCBF.

BP and HR were monitored throughout the experiment (Weco VT -1, Winston Electronics Co., Millbrae, CA) via the right iliac artery.

After a 20 minutes stability period, the baseline of the PCBF, BP and HR was determined during the next 10 minutes; the means were considered 100%. PCBF was measured continuously over 120 minutes with recordings of the mean and standard deviation taken every 5 minutes. BP and HR were recorded every 5 minutes throughout the experiment.

Pancreatitis model and spin-trapping nitrone solution: Acute pancreatitis was induced using 5 X 10^{-6} g/ 1000 g body weight/ h of caerulein (Sigma, St. Louis, MO) i.v. infusion[10]. This infusion began immediately after the baseline measurements.

The PBN (Sigma, St. Louis, MO) compound was used in a dose of 150 mg/ 1000 g body weight. Special precautions were taken during handling the PBN, since it is inactivated by light and air. The PBN was diluted in dimethylsulfate (DMS; Sigma, St. Louis, MO).

Experimental protocol: The animals were divided in four groups of ten. All groups received 0.9% sodium chloride intravenously (0.083 ml/ 1000 g body weight/ min.; Syringe infusion Pump 22, Harvard Apparatus, South Natick, MA) to compensate for insensible losses. This infusion began when the laser-Doppler probe was placed on the pancreas.

Group 1: Animals in the control group received DMS 20 minutes before baseline and 0.9% sodium chloride i.v. after baseline.

Group 2: Animals in the caerulein-induced pancreatitis received DMS 20 minutes before baseline and caerulein solution after baseline.

Group 3: Animals in the PBN group received PBN solution ip 20 minutes before baseline and 0.9% sodium chloride i.v. after baseline.

Group 4: Animals in the caerulein-induced pancreatitis plus PBN group received PBN solution i.p. 20 minutes before baseline and caerulein solution after baseline.

Blood collection, biopsy and analysis: At the end of the experiment arterial blood samples were taken to determine gases (288 Blood Gas System, Ciba-Corning Diagnostics Corp., Medfield, MA) at the Blood Gas Laboratory, Lenox Hill Hospital, New York, NY. Venous blood samples were taken to determine serum amylase, glucose, calcium, sodium, potassium and chloride (Kodak Ektachem 700 XR Analyzer, Eastman Kodak, Rochester, NY) at Lenox Hill Hospital Laboratory, New York, NY.

Pancreatic biopsies were taken from the pancreatic tissue underlying the laser-Doppler probe.

Histophatological analysis: The pancreatic biopsies from forty rats were fixed in Bouin's solution, paraffin embedded and sectioned at 4 microns and then stained with hematoxilin phloxin safran stain. The slides were examined randomly and blindly by two pathologists using a Optiphot Labpot Nikon microscope (Yokohama, Japan). The slides were screened for vacuolation, piknosis and ballooning degeneration. The vacuolation was characterized by the presence of micro and macrovacuolation of the cytoplasm that was normal in color and the granules were distinct. Piknosis and ballooning degeneration was characterized by small foci of piknosis of the nuclei and distention of the cytoplasm becoming pale pink in color with loss of granules.

Statistical analysis: Statistical analysis was performed using PC Statistical Software , (Human Systems Dynamics, Northridge, CA). The results

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are described as the mean ± standard deviation. Student's t-test was employed to make comparison between group means. P values less than 0.05 were considered significant. All PCBF, BP and HR results were expressed in percentage.

RESULTS

The PCBF measured a mean of 109.08 ± 14.54%, 68.24 ± 10.47%, 102.18 ± 10.23% and 87.73 ± 18.72% in groups 1, 2, 3 and 4, respectively. The PCBF measurement did not change significantly ($p>0.05$) in groups 1 and 3 throughout the experiment. The PCBF decreased over time a mean of 31.75 ± 16.79% and 12.26 ± 15.24% in groups 2 and 4, respectively. These PCBF decreases were statistically ($p<0.05$) significant after 20 minutes following baseline for group 2 when compared with group 1. The PCBF increased significantly ($p<0.05$) in group 4 compared with group 3 during the first 20 minutes following baseline, and there was no statistical ($p>0.05$) difference until 60 minutes when a significant ($p<0.05$) decrease was seen. There was a significant ($p<0.05$) increase in the PCBF when compared groups 2 and 4, up to 105 minutes following baseline. No statistical ($p>0.05$) difference was seen in the PCBF between groups 1 and 3. (Fig.1).

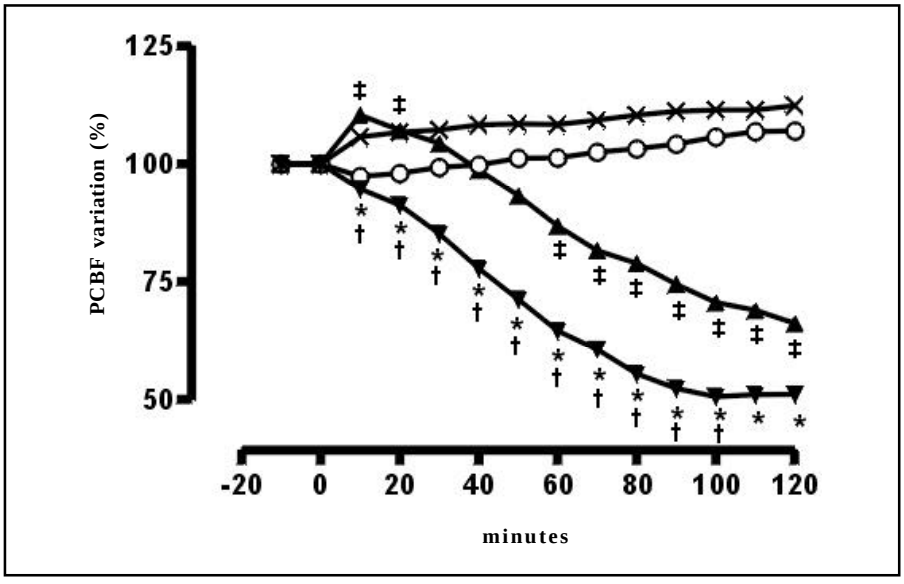

FIGURE 1: Alterations in Pancreatic Capillary Blood Flow (PCBF) in control group (-x--), caerulein group (-▼--),PBN group () and PBN+caerulein group (-▼--). Data are expressed as percentage per minute. No significant ($p>0.05$) changes in PCBF were seen between groups control and PBN. Significant ($p<0.05$) PCBF decrease was seen since the beginning of caerulein-infusion in group 2. The PCBF significantly ($p<0.05$) improved when PBN was employed during caerulein-induced pancreatitis (group 4) mainly during the first 60 minutes after caerulein infusion.

* $p<0.05$ vs control

† $p<0.05$ vs PBN+caerulein

‡ $p<0.05$ vs PBN

PBN (N-tert-phenyl-buthyl-nitrone)

The BP measured a mean of 93.11 ± 9.85%, 108.81 ± 16.43%, 94.37 ± 12.19%, 97.78 ± 17.86% in groups 1, 2, 3 and 4, respectively. The BP increased ($p<0.05$) throughout the experiment only in group 2 and it was significant ($p<0.05$) when compared with group 1.

The HR measured a mean of 102.88 ± 14.80%, 121.42 ± 12.26%, 106.88 ± 10.28%, 100.66 ± 11.24% in groups 1, 2, 3 and 4, respectively. The HR increased significantly ($p<0.05$) throughout the experiment only in group 2 and it was significant ($p<0.05$) when compared with groups 1 and 4.

The serum amylase was 1323.70 ± 239.10 U/l, 2184.60 ± 700.46 U/l, 1379.80 ± 265.72 U/l and 1622.10 ± 314.60 U/l in groups 1, 2, 3 and 4 respectively. There was significant increase ($p<0.01$) when comparing groups 1 and 3 with groups 2 and 4, respectively. There was a significant ($p<0.05$) decrease in the serum amylase when compared groups 2 and 4 (Table I).

The serum glucose, sodium, potassium and chloride results are summarized table I. Results of arterial gases are summarized in table II.

No statistical difference was seen among all groups.

The histopathological study reviewed no qualitative changes in 52.50% of all slides. Vacuolation of the cytoplasm in the acinar cells was found in 3 and 7 slides in groups 2 and 4, respectively. These lesions were isolated in some cases, and multifocal in others. Small foci of piknosis and ballooning degenaration were seen in 6, 1, 3 and 1 slide(s) in groups 1, 2, 3 and 4, respectively. No qualitative difference was seen among groups 1 and 2 when compared with groups 3 and 4, respectively.

TABLE I. Biochemistry Results

	1-Control	2-Caer	3-PBN	4-Caer+PBN
Amylase (U/l)	1323±239*	2184±700*,†	1379±265‡	1622±314†,‡
Calcium (mg/dl)	8.27±0.21	8.60±0.25*	8.40±0.33	8.62±0.23
Sodium (mmol/l)	139±3	143±1	141±2	144±2
Potassium (mmol/l)	5.19±1.03	4.68±0.28	4.99±0.20	5.14±1.02
Chloride (mmol/l)	105±4	106±2	105±2	107±2
Glucose (mg/dl)	350±97*	244±64*	359±91†	242±53†

Caer (ceruleína)
PBN (N-tert-phenyl-buthyl-nitrone)
*, †,‡ ($p<0.05$)

TABLE II. Arterial Blood Gas Results (Room air)

	1-Control	**2-Caer**	**3-PBN**	**4-Caer+PBN**
PH	7.36±0.48	7.40±0.07	7.35±0.04	7.37±0.04
PCO_2 (mmHg)	26.80±4.51	25.50±3.62	28.20±6.64	27.40±6.34
PO_2 (mmHg)	104.90±9.73	101.20±17.62	94.80±17.02	96.70±9.84
HCO_3 (mEq/l)	15.40±1.95	15.40±3.62	15.30±2.58	15.60±2.75
O_2Sat (%)	97.70±0.67	97.70±0.67	96.10±3.92	97.20±1.39

Caer (ceruleína)

PBN (N-tert-phenyl-buthyl-nitrone)

No statistical difference was seen among all groups.

DISCUSSION

Overall, experimental[11] and clinical[12] studies have found that during acute pancreatitis there is a decrease in the blood flow to the pancreas. In our experiment, the PCBF decreased significantly a mean of 31% after 20 minutes of caerulein infusion. It leads us to assume that the PCBF impairment may allow the pancreas to become subject and susceptible to ischemia in this model of pancreatitis. Whether ischemia is a cause or an effect during the course of acute pancreatitis is still controversial. Nevertheless, the important relationship between pancreatic blood flow and the complications following acute pancreatitis should not be underestimated[12]. Ischemia seems to play a key role in the transition from pancreatic edema to necrosis and improvement of capillary perfusion has been shown to be an efficient therapeutic tool[13,14]. Ischemia can serve as an important co-factor to potentiate pancreatitis and convert an incipient insult to the pancreas into a frank pancreatitis[15]. During caerulein-induced pancreatitis, sympathetic excitation induced by water-immersion precipitated hemorrhagic pancreatItIs[16] and phenylephrine exacerbated the acute pancreatitis[17]. Moreover, ischemia has been related with ROS generation[18].

The term ROS defines independent chemical species with one or more unpaired electrons[19]. The unpaired electron determines the instability and reactivity of this species. The reaction of a radical with another molecule forms a new radical leading to a perpetuating chain process. The ROS reactions affect proteins, lipids and nucleic acids[20]. These reactions are influenced by presence and concentration of oxygen, availability of transition metals, level of reductants and antioxidants[21]. When a radical process spreads within a cell, low molecular weight antioxidants (primary damage defense) may interfere with the chain reaction by donating H-atoms to radicals. This results in "reconstitution" of the original radical site. After it becomes a radical itself, the antioxidant may be stable enough to slow the chain process down. So it can await being "healed" by H-atoms derived from metabolism. Vitamin C and E, gluthatione (GSH) and H-atoms from NAD(P)H may be involved in the primary damage control[22]. A secondary damage defense is put forth by GSH-peroxidase, catalase, superoxide dismutase, DT -diaphorase and/or chelators. The final step of defense involves repair processes through lipid degradation/membrane repair enzymes (phospholipases, peroxidases, some transferases and reductases), protein disposal or repair enzymes (proteases, GSSG-reductase) and DNA degradation repair enzymes (exonuclease III, endonucleases III and IV, glycosylases, polymerases). The principal sources of ROS *in vivo* are phagocytes, mitochondrial electron transport system, microsomal electron transport system, solubleoxidase enzymes, autooxidation of endogenous or exogenous substrates and transition metals[20]. Potentially all aerobic cells are capable of producing ROS. ROS have been implicated in the pathogenesis of many conditions[23] such as septic shock, adult respiratory distress syndrome and acute renal failure. Participation in the ischemia-reperfusion organs like myocardial infarction, stroke and organ transplantation seems to be involved with free-radical production[1,2,3]. During ischemic, alcoholic and gallstone pancreatitis animal models, the generation of ROS appears to play a central role in its pathogenesis[5]. In the caerulein-induced pancreatitis model, formation of ROS has also been reported[6].

The N-tert-phenyl-buthyl-nitrone (PBN), a spin-trapping nitrone, was used to determine the presence of ROS during caerulein-induced pancreatitis. A spin-trapping nitrone is a compound that reacts covalently with ROS creating relatively stable radicals[8]. The PBN bioavaibility *in vivo* was demonstrated in various mouse organs[7] and the compound arrives at the sites of ROS generation in a short period of time[4]. No signs of behavioral, parenchymal or local damage were seen during PBN administration over a 7-day period in rats[24].

The PCBF improved during the first 105 minutes following the baseline in group 4 compared with group 2. The overall improvement was a mean of 28.56% in the PCBF when a single PBN dose was added to the caerulein-induced pancreatitis model. Furthermore, the suppression of ROS shows that there was an increase in the PCBF in the first 20 minutes of caerulein infusion when compared group 3 and 4. Also the serum amylase increase in group 2 was statistically reduced in the presence of the PBN. These findings are in accord with reports of gluthatione depletion[25], decrease of superoxide dismutase activity in the pancreatic tissue and elevation malondialdehyde concentration[26] (a by-product of lipid peroxidation) seen during caerulein-induced pancreatitis. During the effort to produce and secret pancreatic enzymes by caerulein hyperstimulation, a disturb in the oxidant-antioxidant balance may occur in the pancreatic cell. Since the presence of polymorfonucleares were not seen in our pathological findings, the mitochondrial system and the microsomal electron transport system are most likely be involved in the ROS generation. The result is a leaking of ROS from these sites leading to lipid peroxidation and consequent membrane cell damage. This hypothesis agrees with marked changes in the Golgi complex and mitochondrias described during caerulein-induced pancreatitis[10]. The increase in capillary permeability and vascular reactivity has been attributed to ROS generation[4,27]. Similar morphological alterations were found in the hepatic sinusoids[28,29] suggesting that caerulein-induced pancreatitis is associated with extrapancreatic microvascular damage. In addition, acute lung injury[30] and hepatic impairment[31] associated with caerulein-induced pancreatitis appears in part to be mediated by ROS. Therefore, the edema formation and PCBF decrease, at least in part, may be attributed to ROS generation.

In conclusion, our findings suggest that ROS generation has a early onset and may be related with PCBF decrease during caerulein-induced pancreatitis model. The ROS inactivation by PBN improves PCBF and minimizes the serum amylase increase during caerulein-induced pancreatitis. The ROS inactivation may be helpful both in improving the PCBF and decreasing the local and systemic complication following caerulein-induced acute pancreatitis.

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RESUMO – Objetivo: A inativação de radicais livres (RL) foi estudada para determinar as alterações do fluxo capilar pancreático (FCP) na pancreatite aguda induzida por ceruleína em ratos.**Métodos:** Um laser-Doppler fluxímetro determinou o FCP e o composto N-t-Butyl-Phenylnitrone (PBN), para inativar os RL, foi utilizado. Quarenta ratos foram divididos em 4 grupos: 1) controle; 2)ceruleína; 3) PBN; 4)ceruleína+PBN. Dosagens bioquímicas e análise histopatológica foram realizadas. **Resultados:** O FCP foi em média 109.08 ± 14.54%, 68.24 ± 10.47%, 102.18 ± 10.23% e 87.73 ± 18.72% nos grupos 1, 2, 3 and 4, respectivamente. O FCP nos grupos 2 e 4 diminuíram em média 31.75 ± 16.79% e 12.26 ± 15.24%, respectivamente. A média da amilase sérica foi de 1323,70 ± 239.10 U/l, 2184,60 ± 700,46 U/l, 1379,80 ± 265,72 U/l e 1622,10 ± 314,60 U/l nos grupos 1, 2, 3 e 4, respectivamente. Observou-se diferença significante no FCP e na amilase sérica quando comparados os grupos 2 e 4. Vacuolização citoplasmática estava presente nos grupos 3 e 4. Não foram observadas outras alterações qualitativas. **Conclusão** A inativação de RL melhorou o FCP e minimizou a elevação da amilase sérica na pancreatite aguda induzida por ceruleína. A presença de RL parece ser um evento precoce neste modelo de pancreatite aguda experimental.

DESCRITORES: Fluxo sanguíneo. Ceruleína. Laser-Doppler. Radicais de oxigênio.

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Community acquired urinary tract infection: etiology and bacterial susceptibility[1]

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