aware that this kind of variation is more prone to injury in surgical operations of the axilla and that, the very close course of the second lateral root of the median nerve to the axillary artery may lessen the blood supply of the upper extremity by compressing the vessel[3].

Although some differences were present in our material, a pattern of variations for sex, color or side of the body was not evident. As also described by Kerr[8], the plexuses studied did not show that sex, color or side of the body had much if any influence upon the presence of variations.

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**RESUMO – Objetivos:** O plexo braquial apresenta uma estrutura anatômica complexa, desde sua origem, no pescoço, até sua ramificação terminal, na região axilar. Ele também apresenta relações importantes com outras estruturas anatômicas locais, o que o torna vulnerável ao aparecimento de uma série de variações anatômicas, marcando sua importância clínica e cirúrgica. Os objetivos desse estudo foram de descrever as variações anatômicas do plexo braquial, desde sua origem até seus ramos terminais e correlacionar essas variações com o sexo e a cor dos indivíduos, bem como com o lado do corpo estudado. **Métodos:** Vinte e sete cadáveres adultos, separados em sexo e cor, tiveram seus plexos braquiais avaliados à direita e à esquerda. **Resultados:** Nossos resultados são extensos e descrevem um grande número de variações, incluindo algumas ainda não descritas na literatura. Nossos resultados mostram que o nervo frênico apresentou sua origem diretamente no plexo braquial em 20% dos casos. Assim, uma lesão das raízes do plexo braquial poderia resultar em uma inexplicada paralisia diafragmática. Não é esperado que o nervo torácico longo passe através do músculo escaleno médio entretanto, esse fato foi observado em 63% de nossos casos. Outra observaçõa foi a formação do fascículo posterior pelas divisões posteriores dos troncos superior e médio em 9% dos casos. Nesses casos, os nervos axilar e radial poderão não receber fibras de C7 e C8, como normalmente descrito na literatura. **Conclusão:** Os plexos braquiais estudados não mostraram que o sexo, a cor ou o lado do corpo influenciam de maneira importante na presença de variações anatômicas dessa estrutura.



**DESCRITORES:** Anatomia. Axila. Plexo braquial. Variações anatômicas. Nervos periféricos.



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7 – ARTIGO ORIGINAL

# Pancreatic capillary blood flow during caerulein-induced pancreatitis evaluated by a laser-doppler flowmeter in rats


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**ABSTRACT – Purpose:** The pancreatic capillary blood flow (PCBF) was studied to determine its alterations during caerulein-induced pancreatitis in rats. **Methods:** Twenty rats were divided in groups: control and caerulein. A laser-Doppler flowmeter to measure PCBF continuously was used. Blood pressure (BP) and heart rate (HR) were monitored. Serum biochemistry analyses were determined.

Histopathological study was performed. **Results:** The PCBF measured a mean of 109.08 ± 14.54% and 68.24 ± 10.47% in control group and caerulein group, respectively. Caerulein group had a mean decrease of 31.75 ± 16.79%. The serum amylase was 1323.70 ± 239.10U.$I^{-1}$ and 2184.60 ± 700.46U.$I^{-1}$ in control and caerulein groups, respectively. There was a significant difference in the PCBF ($p<0.05$) and serum amylase ($p<0.05$) when compared to control and caerulein groups. Although micro and microvacuolization were seen in 30% in caerulein group, no significant difference was seen between the groups. **Conclusion:** A decrease in the PCBF may be one of the leading events and it is present before histopathological tissue injury had been established in this model of acute pancreatitis.

**KEY WORDS –** Blood flow. Caerulein. Pancreatitis. Laser-Doppler.

## INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems[1,2]. Its clinical features are severe upper abdominal pain associated with vomiting, leukocytoses and increase of pancreatic enzymes[1,2,3].

Pancreatic blood flow seems to be involved in the pathogenesis of AP. Pancreatic blood flow impairment is an important mechanism in the transition of edematous to necrohemorrhagic pancreatitis[4]. Although changes in the pancreatic blood flow during AP are well reported[4,5,6,7], the initial mechanisms involving its pathogenesis remains poorly understood[8]. Besides, it is unclear whether the pancreatic capillary blood flow (PCBF) changes are cause or consequence of the AP[5].

The purpose of this experiment was to study pancreatic capillary blood flow PCBF changes, using a laser-Doppler flowmeter, (LDF) during caerulein-induced pancreatitis.

## METHODS

Surgical preparation: Twenty Sprague-Dawley male rats weighing between 320 and 410 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 -36.6º C using a thermo controller (made by Béla Kurucz, E.E., Maglód, Hungary). An arterial and venous line were 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 two 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 control:*** Animals in the control group received DMS 20 minutes before baseline and 0.9% sodium chloride i.v. after baseline.

Group caerulein: Animals in the caerulein-induced pancreatitis received DMS 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 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

PCBF measured a mean of 109.08 ± 14.54%, 68.24 ± 10.47% in control and caerulein groups, respectively. The PCBF measurement did not change significantly ($p>0.05$) in control group throughout the experiment. The PCBF decreased over time a mean of 31.75 ± 16.79% in caerulein group. These PCBF decreases were statistically ($p<0.05$) significant after 20 minutes following baseline for caerulein group when compared with control group. (Fig.1).

The BP measured a mean of 93.11 ± 9.85%, 108.81 ± 16.43% in control and caerulein groups, respectively. The BP increased ($p<0.05$) throughout the experiment only in caerulein group and it was significant ($p<0.05$) when compared with control group.

The HR measured a mean of 102.88 ± 14.80%, 121.42 ± 12.26% in control and caerulein groups, respectively. The HR increased significantly ($p<0.05$) throughout the experiment only in caerulein group and it was significant ($p<0.05$) when compared with control group.

The serum amylase was 1323.70 ± 239.10 U/l, 2184.60 ± 700.46 U/l in control and caerulein groups, respectively. There was significant increase ($p<0.01$) when comparing control group with caerulein group. (Table I).

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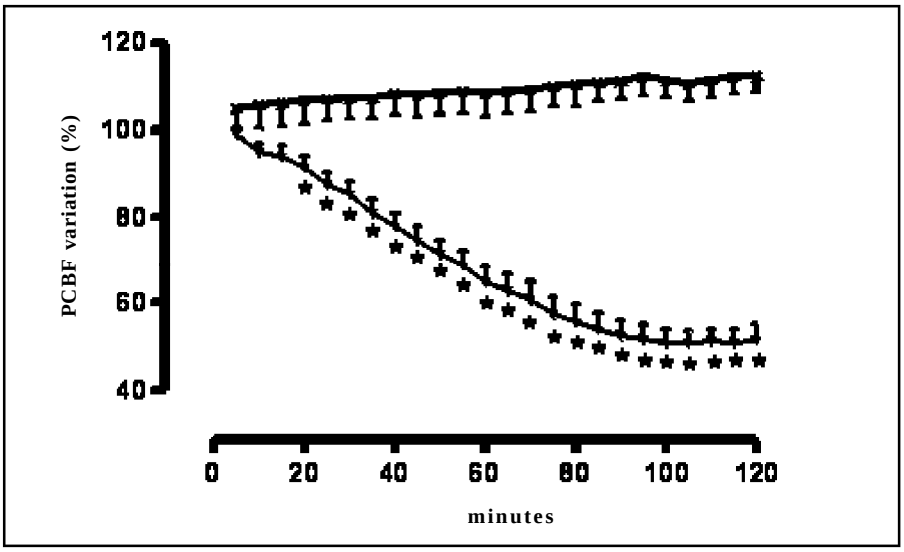


**FIGURE 1:** Alterations in Pancreatic Capillary Blood Flow (PCBF) in control group (--X--) and caerulein group (--▼--). Data are expressed as percentage per minute. Significant ($p<0.05$) PCBF decrease was seen 20 minutes after beginning caerulein-infusion.
*$p<0.05$ vs control

**TABLE I**. Biochemistry Results

| | 1-Control | 2-Caerulein |
|---|---|---|
| Amylase (U/l) | 1323±239 | 2184±700* |
| Calcium (mg/dl) | 8.27±0.21 | 8.60±0.25* |
| Sodium (mmol/l) | 139±3 | 143±1 |
| Potassium (mmol/l) | 5.19±1.03 | 4.68±0.28 |
| Chloride (mmol/l) | 105±4 | 106±2 |
| Glucose (mg/dl) | 350±97 | 244±64* |

*$p<0.05$

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

**TABLE II**. Arterial Blood Gas Results (Room air)

| | Control | Caerulein |
|---|---|---|
| pH | 7.36±0.48 | 7.40±0.07 |
| PCO2 (mmHg) | 26.80±4.51 | 25.50±3.62 |
| PO2 (mmHg) | 104.90±9.73 | 101.20±17.62 |
| HCO3 (mEq/l) | 15.40±1.95 | 15.40±3.62 |
| O2Sat (%) | 97.70±0.67 | 97.70±0.67 |

No statistical difference was seen among all groups.

The histopathological study reviewed no qualitative changes in 30% of all slides. Vacuolation of the cytoplasm in the acinar cells was found in 3 slides in caerulein group. These lesions were isolated in some cases, and multifocal in others. Small foci of piknosis and ballooning degenaration were seen in 6 and 1 slide(s) in control and caerulein groups, respectively. No qualitative difference was seen between groups.

## DISCUSSION

The importance of blood flow in the pathogenesis of acute pancreatitis has been investigated since 1862 by Panum when pancreatic hemorrhage was induced by injecting small particles of wax into the pancreatic artery of experimental animals[11]. Caerulein-induced pancreatitis is characterized by acinar cell damage and interstitial edema[10,12]. Enclosure of intracellular organelles within autophagic vacuoles with subsequent lysosomal degradation appears to contribute to the destruction of the acinar cells in this model of acute pancreatitis[12,13]. During caerulein-induced pancreatitis there is a collapse in the pancreatic capillaries and surface blebbing, formation of cytoplasmatic vacuoles, edema, and swollen mitochondria in the endothelial cells[14,15,16]. These structural alterations were present early in the experimental edematous pancreatitis[14]. Overall, experimental[17] and clinical[5] 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[5]. 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[4,18]. Ischemia can serve as an important co-factor to potentiate pancreatitis and convert an incipient insult to the pancreas into a frank pancreatitis[8]. During caerulein-induced pancreatitis, sympathetic excitation induced by water-immersion precipitated hemorrhagic pancreatitis[19] and phenylephrine exacerbated the acute pancreatitis[20]. In this study, supramaximal caerulein infusion ($5 \times 10^{-6}$ g.kg$^{-1}$ body weight.h$^{-1}$) caused serum amylase and calcium increase with hipoglicemia. The PCBF decreased associated with increased BP and HR. Early findings of vacuolation were present in 30% of the caerulein group.

The caerulein effects in the pancreas are dosage and time related[20]. In caerulein-induced AP the PBF determined by LDF it is decreased from 43% to 51% after 2-5 hours of caerulein infusion in rats[1,22]. When H2-clearence technique is used to determine PBF, caerulein doses at 0.5, 10 and 40 µg.kg$^{-1}$.h$^{-1}$ there is also a decrease in PBF by 30 to 40% after 5 hours of AP in rats[23,24,25,26]. However, doses of 5 and 20 µg.kg$^{-1}$.h$^{-1}$ showed an increase in PBF[23]. In that study, there was a volemic replacement with a crystalloid infusion rate three times higher than our study. Besides, normovolemia does not represent the AP natural clinical evolution where there is intravascular fluid depletion due to increased capillary permeability[14].

Nevertheless, experimental studies using dogs presented increased PBF after caerulein-induced AP[27,28,29] and increase[18] as well decrease[30] in PBF when rabbits.

The impairment of PBF associated to increased BP and HR might be an adrenergic response due to caerulein infusion, the caerulein direct effect in the pancreas or vasoactive substances released from the inflamed pancreas. The caerulein circulatory effect is known and it is specie dependent. In rats, there is an increase in BP, as seen in the caerulein group. In humans, there is arterial hypotension following caerulein infusion[31]. In our study, both groups were submitted to the same method, differing only by the caerulein infusion, thus the adrenergic response may not be directly responsible by decreasing PCBF. Furthermore, there was no correlation over time among increasing BP and HR with decreasing PCBF. BP and HR remained increased from the beginning of the experiment

while PCBF had a progressive decrease after 20 minutes of caerulein infusion.

The beginning of PCBF decrease is in accordance with early acinar intracellular changes seen after 15 minutes of caerulein infusion[32]. Electron microscopy showed endothelial injury such as vascular degeneration, disorganized intracellular junctions, perivascular edema and vascular occlusion during caerulein-incuced AP. Early edema formation is due to increased capillary permeability in caerulein-induced AP[14].

Platelet activation factor (PAF) seems to be directly involved in caerulein-induced AP pathogenesis. PAF inhibitors attenuate hyperamylasemia, edema formation and improve histopathological changes in this AP model[33]. PAF impairs pancreatic microcirculation in early phases of caerulein-induced AP. PCBF decreased before we could identify edema and leukocyte infiltration in the histopathological study.

The decreased glucose serum levels seen after AP induction is a caerulein modulating insulin output effect in the pancreatic beta-cells[34]. Caerulein promotes insulin releasing by interaction with beta-cells receptors[35,36].

In conclusion, a decrease in the PCBF may be one of the leading events and it is present before histopathological tissue injury had been established in this model of acute pancreatitis. Future experimental investigations should address what are the causes leading to early PCBF impairment such as PAF, free radicals, TNF-a, and nitric oxide.

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**RESUMO – Objetivo:** O fluxo capilar pancreático (FCP) foi estudado para determinar suas alterações durante a pancreatite aguda induzida por ceruleína, em ratos. **Métodos:** Vinte ratos foram divididos em grupo controle e grupo ceruleína. Um laser-Doppler fluxímetro foi empregado para determinar, continuamente, o FCP durante 120 minutos. A pressão arterial média (PAM) e a freqüência cardíaca (FC) foram determinadas, durante o experimento. Análise bioquímica sérica e estudo histopatológico, por microscopia ótica, do tecido pancreático foram realizados, ao final do experimento. **Resultados:** O FCP foi em média 109,08 ± 2,17% e 68,24 ± 16,79% nos grupos controle e ceruleína , respectivamente. No grupo ceruleína, houve uma diminuição média de 31,75 ± 16,79%. Os níveis de amilase sérica foram de 1323,70 ± 239,10U.$I^{-1}$ e 2184,60 ± 700,46U.$I^{-1}$ nos grupos controle e ceruleína, respectivamente. Houve diferença significante ($p<0,05$) no FCP e na amilasemia, quando comparado o grupo controle com o grupo ceruleína. Embora micro e macrovacuolização estivessem presentes no grupo ceruleína, não houve diferença histológica entre os grupos. **Conclusão:** A diminuição do FCP parece um evento precoce, antecedendo o aparecimento de alterações histopatológicas, por microscopia ótica, que caracterizam este modelo de pancreatite edematosa aguda.

**DESCRITORES:** Fluxo sanguíneo. Ceruleína. Pancreatite. Laser-Doppler.

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# Free PSA and prostate volume on the diagnosis of prostate carcinoma[1]

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**ABSTRACT – Objective:** To analyse the influence of prostate volume on the performance of total prostate specific antigen (tPSA) and free PSA (fPSA) on the diagnosis of prostate adenocarcinoma. **Methods:** A total of 188 patients underwent transrectal ultrasound guided biopsies (10-12 cores) due to prostate nodes detected by digital rectal examination and/or tPSA range of 2.5-10ng/ml. Mean age was 65.7±8.7 years. 19/100 (19%)(GI) patients with prostate volume >40ml had prostate cancer while the corresponding figure for patients with prostate <40ml was 26/88 (29.5%)(GII). We analyzed the sensitivity and specificity of tPSA at cut-off points of 2.5 and 4ng/ml as well as the influence of the ratio f/tPSA in both groups of patients. **Results:** In the group GI tPSA sensitivity and specificity were 94.4% and 19.5% at the cut-off level of 4ng/ml and 100% and 6% at 2.5ng/ml. The corresponding values for GII were 76.5% and 62.9%, and 100% and 19.3%. In group GI a cut-off of 19% for the ratio f/tPSA kept tPSA sensitivity over 90% while the specificity increased to 46.2% at cut-off level of 4ng/ml and to 32.9% at 2.5ng/ml. In the group GII the ratio f/tPSA was not able to increase the specificity of tPSA at a cut-off level of 4ng/ml without an expressive reduction of sensitivity. On the other side, for this group a cut-off of 16% for the f/tPSA ratio rose the specificity to 46.7% for a sensitivity over 90%. **Conclusion:** We recommend stratification of patients according to prostate volume to define tPSA cut-off point. The cut-off level of 2.5ng/ml for tPSA combined with f/tPSA ratio of 19% in prostates >40ml and 16% in prostates <40ml was a better option for prostate biopsy indication than tPSA at a cut-off of 4ng/ml associated or not with f/tPSA ratio.

**KEY WORDS:** Prostate specific antigen. Prostate. Carcinoma. Adenocarcinoma. Screening.

## INTRODUCTION

The prostate specific antigen (PSA) is a kallicrein controlled by a gene on cromossome 19. It is a glicoprotein produced by the prostate epithelium which fuction is to promote semen liquefation[1,2]. In the plasma PSA circulates free or complexed with proteins: a1-antichemotrypsin (ACT) and a2-macroglobulin (MG). There are several types of assay to determine PSA level in the serum and the most common are able to measure the total PSA (tPSA) and the free PSA (fPSA).

Approximately 30% of the patients with tPSA between 4-10ng/ml bear prostate adenocarcinoma while 20% of tumors occur in

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