# Effect of L-norvaline on the small intestinal wall blood perfusion in a model ofacute segmental mesenteric thrombosis

*Effecto de L-norvalina en la perfusión sanguínea de la pared del intestino delgado en el modelo de trombosis mesentérica segmentaria aguda*

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## Abstract

**Introduction.** Ischemic and reperfusion injury play one of the most important roles in the pathogenesis of many disorders. Especially severe changes in the wall of the small intestine are observed in acute mesenteric thrombosis, and restoration of blood flow to the ischemic tissue initiates a cascade of events that may lead to additional cell injury known as reperfusion injury. This reperfusion damage frequently exceeds the original ischemic insult. L-norvaline, as an arginase inhibitor was shown to be potentially strategy to combat hepatic ischemic/reperfusion injury. However, the use of this drug to protect the small intestine from ischemia is not currently studied.

**Objective.** This research aimed to study the effect of L-norvaline, an arginase inhibitor, on the small intestinal wall blood perfusion in a model of acute segmental mesenteric thrombosis.

**Material and Methods.** The experiment was performed on 60 female white Wistar rats, weighing 200-250 g. All studies were performed in compliance with the rules of humane treatment of animals. The animals were divided into 6 groups of 10 animals each. L-norvaline was administered intraperitoneally in dosages of 5, 10, 15, and 20 mg/kg, 30 minutes before occlusion of segmental mesenteric arteries. The speed of microcirculation was measured using laser Doppler flowmetry by Biopac systems MP100 with TSD144 probe and Acknowledge 3.9.0 program.

**Results.** Arginase inhibitor, L-norvaline, in doses of 5, 10, 15, 20 mg/kg decreased the level of post-occlusive hyperemia from 1846.25± 54.97 BPU to 1738.49± 42.67, 1622.91± 17.15, and 1412,88 ± 38,08 BPU, respectively. Also, L-norvaline increased blood velocity during the first minute of reperfusion.

**Conclusion.** The use of L-norvaline in the model of acute segmental mesenteric thrombosis with subsequent removal of blood clot has a significant protective effect leading to an increase of microcirculation blood velocity in the first minute of reperfusion with a decrease in the level of transient hyperemia, and this protective action has a clear dose-dependent effect, which is maximally manifested in the dose range of 15-20 mg/kg.

**Keywords:** L-norvaline, mesenteric thrombosis model, intestinal ischemia, reperfusion.



## Resumen

**Introducción**: La lesión isquémica y de reperfusión desempeña uno de los papeles más importantes en la patogénesis de muchos trastornos. Se observan cambios especialmente graves en la pared del intestino delgado en la trombosis mesentérica aguda, y la restauración del flujo sanguíneo al tejido isquémico inicia una cascada de eventos que pueden conducir a una lesión celular adicional conocida como lesión por reperfusión. Este daño por reperfusión frecuentemente excede el insulto isquémico original. La L-norvalina, como inhibidor de la arginasa, demostró ser una estrategia potencial para combatir la lesión hepática por isquemia/reperfusión. Sin embargo, el uso de este medicamento para proteger el intestino delgado de la isquemia noha sido estudiado aun.

**Objetivo**: Esta investigación tuvo como objetivo estudiar el efecto de la L-norvalina, un inhibidor de la arginasa, sobre la perfusión sanguínea de la pared del intestino delgado en un modelo de trombosis mesentérica segmentaria aguda.

**Material y métodos**: El experimento se realizó en 60 ratas Wistar blancas hembras, con un peso de 200-250 g. Todos los estudios se realizaron de conformidad con las normas de trato humano de los animales. Los animales se dividieron en 6 grupos de 10 animales cada uno. L-norvalina se administró por vía intraperitoneal en dosis de 5, 10, 15 y 20 mg/kg, 30 minutos antes de la oclusión de las arterias mesentéricas segmentarias. La velocidad de la microcirculación se midió utilizando la flujometría láser Doppler mediante los sistemas Biopac MP100 con sonda TSD144 y el programa Acknowledge 3.9.0.

**Resultados:** El inhibidor de la arginasa, L-norvalina, en dosis de 5, 10, 15, 20 mg/kg, disminuyó el nivel de hiperemia post-oclusiva de 1846.25±54.97 BPU a 1738.49±42.67, 1622.91±17.15 y 1412,88±38,08 BPU, respectivamente. Además, la L-norvalina aumentó la velocidad de la sangre durante el primer minuto de reperfusión.

**Conclusión:** El uso de L-norvalina en el modelo de trombosis mesentérica segmentaria aguda con la posterior eliminación del coágulo sanguíneo tiene un efecto protector significativo que conduce a un aumento de la velocidad de la microcirculación sanguínea en el primer minuto de reperfusión con una disminución en el nivel de hiperemia transitoria, y esta acción protectora tiene un claro efecto dependiente de la dosis, que se manifiesta al máximo en el rango de dosis de 15-20 mg kg.

**Palabras clave:** L-norvalina, modelo de trombosis mesentérica, isquemia intestinal, reperfusión.

## Introduction

Ischemic and reperfusion lesions play one of the most important roles in the pathogenesis of many diseases[1-4]. The small intestine is no exception, and a decrease in blood flow, even for a short time, is manifested by significant morphofunctional changes[5-8]. Especially severe changes in the wall of the small intestine are observed in acute mesenteric thrombosis, and restoration of blood flow to the ischemic tissue initiates a cascade of events that may lead to additional cell injury known as reperfusion injury. This reperfusion damage frequently exceeds the original ischemic insult[9-10]. The discovery of ischemic preconditioning became a new stage in understanding the implementation of the protective influence of various factors and served as a starting point in the search for a pharmacological agent that implements its action on the mechanisms of ischemic preconditioning[3,11-12]. The possible pharmacological modeling of the powerful protective action of ischemic preconditioning now is of great interest[12-13].

One of the substances that model the effect of distant ischemic preconditioning, its second window, is L-norvaline[14-16]. However, the use of this drug to protect the small intestine from ischemia is not currently studied.

The development of new strategies and principles in the pharmacological correction of pathological processes requires a whole set of methodological approaches in the study and correction including molecular, tissue, and organ levels, studies of toxicity, and influence on embryogenesis[17-20].

One of the promising directions in the correction of pathological processes of character is the use of antimediatory drugs and antimetabolites and highly specific and selective blockers[21-25,32]. This research aimed to study the effect of L-norvaline, an arginase inhibitor, on the small intestinal wall blood perfusion in a model of acute segmental mesenteric thrombosis.

## Material and Methods

The experiment was performed on 60 female white Wistar rats, of the same age weighing 200-250g. All studies were performed in compliance with the rules of humane treatment of animals. For the study, were used rats without external signs of the disease, which passed the quarantine regime and were kept in standard conditions.

The animals were divided into the following groups:

- group A: normal values (10 animals).
- group B: Control group (10 animals) - a group in which segmental mesenteric thrombosis was modeled by clipping segmental small bowel arteries for 30 minutes, followed by removal of the clip and an episode of 30-minute reperfusion.
- group C: a group (10 animals) which received L-norvaline at a dose of 5 mg/kg, during 30-minute segmental occlusion of the small intestine arteries followed by 30-minute reperfusion.
- group D: a group (10 animals), which received L-norvaline at a dose of 10 mg/kg during a 30-minute segmental occlusion of the small intestine arteries followed by 30-minute reperfusion.
- group E: a group (10 animals), which received L-norvaline at a dose of 15 mg/kg during a 30-minute segmental occlusion of the small bowel arteries followed by 30-minute reperfusion.
- group F: a group (10 animals), which received L-norvaline at a dose of 20 mg/kg during a 30-minute segmental occlusion of the small intestine arteries followed by 30-minute reperfusion.

• In Figure 1 is shown the protocol of the experiment.

The level of microcirculation was determined using the Biopac systems MP100 equipment with the LDF100C laser Doppler flowmetry module and the tsd144 invasive needle probe with recording and processing in the Acqknowledge 3.9.0 program.

Statistical analysis of the data was carried out using Microsoft Excel version 2007. The data were expressed as mean (M) of indicators and the standard error of the mean (m), and the confidence criterion (p). Differences were considered statistically significant at values p≤0.05.

All manipulations were performed under general anesthesia by intraperitoneal injection of zoletil, at a dose of 60 mg/kg and chloral hydrate at a dose of 125 mg/kg.

Acute mesenteric thrombosis was modeled by occluding the first 4 segmental small intestine arteries for 30 minutes; the absence of blood flow was controlled using LDF. Effective occlusion was compression, in which microcirculation decrease to undetectable values. The drug was administered 30 minutes before the start of the experiment to implement its action[14].

**Figure 1. The protocol of the experiment**

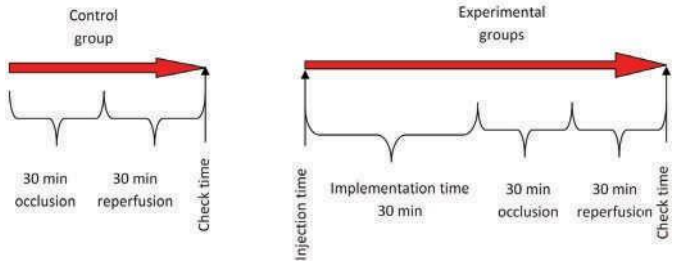
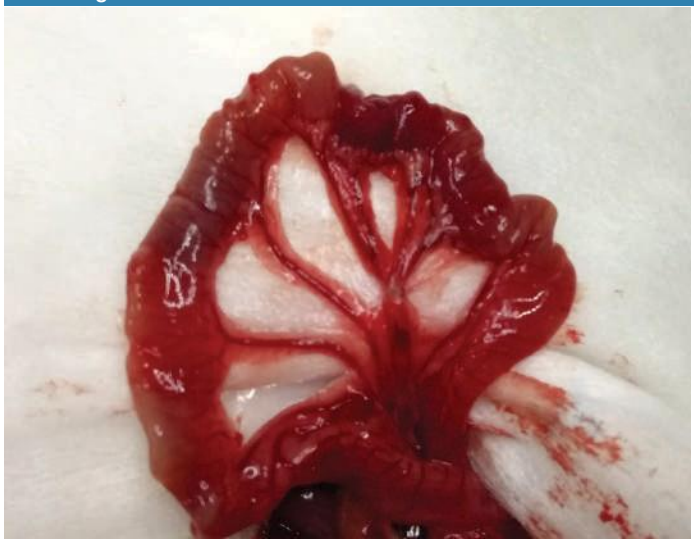



**Figure 2. Segmental mesenteric thrombosis model with occluded 4 segmental arteries.**





## Results and Discussion

During the study, it was found that during an episode of ischemia, the rate of volumetric blood flow decreases from 522.73±51.13 BPU of the intact group to almost zero, and when the blood flow was restored, there was pronounced hyperemia with an increase in blood flow in the first minute to the level of 106.38±13.23 BPU, and by 15 minutes reaching 1846.25±54.97 BPU, by 30 minutes decreasing to the level of 628.73±36.48 BPU.

When L-norvaline was administered intraperitoneally, at a dose of 5mg/kg 30 minutes before mesenteric vascular occlusion, it increased the rate of volumetric perfusion of small intestine tissues to the level of 116.31±5.14 PE at the first minute of reperfusion, with an increase to 1738.49±42.67 PE at 15 minutes and a subsequent decrease to 603.29±19.37 PE at 30 minutes. When compared with the control group, there was a slight increase in the initial volume rate of reperfusion by 9.3%, the level of transient hyperemia decreases by 6.1%, and by 30 minutes, the rate of volume perfusion of small intestine tissue is 4.2% lower than in the control group.

When L-norvaline was intraperitoneally administered, at a dose of 10 mg/kg, 30 minutes before the episode of mesenteric vascular occlusion with subsequent reperfusion, we observed an increase in the rate of volumetric perfusion of small intestine tissues to the level of 129.21±12.13 PE at the first minute of reperfusion, with an increase to 1622.91±17.15 PE at 15 minutes and a subsequent decrease to 587.05±9.64 PE at 30 minutes. As a percentage, this is expressed in an increase in the rate of reperfusion at 1 minute by 21.4% and a decrease in the value of transient hyperemia at 15 and 30 minutes by 13.7% and 7.0%, respectively.

Group E, in which L-norvaline was administered at a dose of 15 mg/kg to correct the pathological effect of mesenteric vascular occlusion, was characterized by perfusion in the small intestine segment at the level of 169.34±15.08 PE, increasing to 1412.88±38.08 PE by 15 minutes, and decreasing to 527.08±19.26 PE by 30 minutes.

Administration of L-norvaline at a dose of 20 mg/kg 30 minutes before the episode of mesenteric vascular occlusion induced a decrease in transient hyperemia, so the blood flow rate at the first minute of reperfusion in this group was 173.37±18.94 PE, by 15 minutes increasing to 1368.88±48.64 PE, and by 30 minutes decreasing to 492.19±17.35 PE.

When comparing the effect of L-norvaline on small intestine perfusion at dosages of 15 and 20 mg/kg, it was found that the greatest increase in the rate of reperfusion is observed in group F (20mg/kg) was 62.9%, but the use of L-norvaline at a dose of 15 mg/kg causes a comparable increase in reperfusion in the first minute by 59.1% compared to the control group.

This statement is also true for transient hyperemia where it is reduced by 30.6% and 34.8% in groups E (15 mg/kg) and group F (20 mg/kg). This difference becomes more significant by the time of 30 minutes, reaching 19.2% and 27.7%, respectively (Table 1).

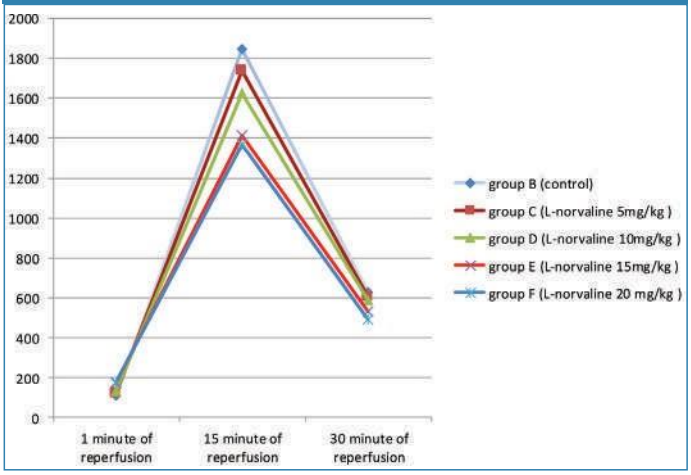
**Table 1. Influence of L-norvaline administration at the model of segmental mesenteric thrombosis and blood flow recovery**

| Group | 1 minute of reperfusion | 15 minute of reperfusion | 30 minute of reperfusion |
|---|---|---|---|
| Group B (control) | 106.38±13.23 | 1846.25±54.97 | 628.73±36.48 |
| Group C (L-norvaline 5mg/kg ) | 116.31±5.14* | 1738.49±42.67* | 603.29±19.37* |
| Group D (L-norvaline 10mg/kg ) | 129.21±12.13* | 1622.91±17.15* | 587.05±9.64* |
| Group E (L-norvaline 15mg/kg ) | 169.34± 15.08* | 1412.88 ± 38.08* | 527.08± 19.26* |
| Group F (L-norvaline 20 mg/kg ) | 173.37± 18.94* | 1368.88 ± 48.64* | 492.19± 17.35* |

Note. * p <0.05 - the significance of differences with the control group

The dynamics of perfusion indicators are clearly shown in figure 3. Such dynamics indicate a significant protective effect of the L-Norvaline, an arginase inhibitor, in the modeling of acute segmental mesenteric thrombosis and thrombus extraction.

**Figure 3. Intestinal perfusion dynamic during the model of mesenterial thrombosis model in L-norvaline action**




Even though there is evidence L-Norvaline usage for tissue protection in ischemia and reperfusion, studies of the effect of this drug on small intestine ischemia have not been identified in the available literature. In this respect, our results are consistent with the results of other investigations, and therefore we assume that the implementation of the L-norvaline protective mechanism action lies in the area of modeling the second window of ischemic preconditioning and consists in increasing the synthesis of nitric oxide. The most interesting question is the direct implementation of the protective mechanism, as research in recent years suggests that it is a decrease in the partial pressure of oxygen in tissues that leads to the production of Hifa, which in turn triggers an increase in the expression of NO-synthase[7,26]. Although it was previously assumed that a change in the concentration of nitric oxide leads to an increase in the synthesis of a factor induced by hypoxia[27-31,33].

## Conclusion

The use of L-norvaline in the model of acute segmental mesenteric thrombosis with subsequent extraction of blood clot has a significant protective effect leading to an increase of microcirculation blood velocity in the first minute of reperfusion with a decrease in the level of transient hyperemia, and this protective action has a clear dose-dependent effect, which is maximally manifested in the dose range of 15-20 mg/kg.

### Main Findings

1. Administration of L-norvaline intraperitoneally, 30 minutes before occlusion of mesenteric arteries significantly decreases post-ischemic hyperemia.
2. The protective influence of L-norvaline has a dose-dependent effect with a maximum of action at a dose of 15-20 mg/kg

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