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ORIGINAL ARTICLE

# MESENTERIC ISCHEMIA AS A CAUSE OF EARLY DEATH AMONG MICE INFECTED BY *Schistosoma mansoni*

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## ABSTRACT

Laboratory maintenance of the *Schistosoma mansoni* cycle is necessary for developing studies regarding the diagnosis, treatment and control of schistosomiasis. Within this perspective, it is paramount that mice infected by the parasite should present a minimum survival of six months. However, between October 2016 and May 2017, early deaths were observed among infected animals kept in the vivarium of the Schistosomiasis Reference Service of IAM-FIOCRUZ. Therefore, the purpose of the present study was to present the results obtained after investigating the main cause of death among these animals. To achieve this, animals that died or that needed to be euthanized due to clinical distress caused by parasite infection were necropsied to investigate the cause of death and clinical condition. Fragments from the intestines, mesenteric vessels and livers were removed and were subjected to histopathological studies. In addition, mouse feces were collected and analyzed using the hydrogen peroxide reaction to detect occult blood. Over an eight-month period, 70 deaths were noted. Forty two animals presented mesenteric ischemia, a vascular insufficiency syndrome that causes a reduction in the nutrient supply to the intestinal viscera. There is, therefore, a need to reduce the infective parasite load in mice to increase their survival, reduce distress caused by the infection and ensure maintenance of the *S. mansoni* cycle, thus enabling continuity of scientific studies on this parasitosis.

KEY WORDS: Mesenteric vascular occlusion; ischemia; *Schistosoma mansoni*; mice.

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## INTRODUCTION

Schistosomiasis is a parasitic disease in which the parasite, *S. mansoni*, initially inhabits the hepatic portal system, where it develops until the adult stage. It then mates and migrates to mesenteric vessels and venules that irrigate intestinal walls. This is where females deposit their eggs, which block and disarrange the local blood flow, along with the extrusion of eggs into the surrounding tissue (Rey, 2011). The physiopathology of this disease is associated with tissue lesions caused by penetration of eggs into tissues, which especially affects the intestine, liver and spleen. This causes congestion of veins in the intrahepatic portal system that can be worsened by the presence of adult worms in the vessels (Knobel, 1994).

In human infections, this vein congestion causes a clinical manifestation that is common in chronic forms of the disease: portal hypertension. However, a severe occlusion characteristic of mesenteric ischemia is rare. This form of ischemia is a syndrome caused by vascular insufficiency of the celiac trunk and/or superior and inferior mesenteric artery that obstructs blood flow and causes reductions in the nutrient supply to the corresponding organs. However, when mesenteric ischemic syndromes occur, these can be either occlusive or non-occlusive and may present both acute and chronic forms, of either arterial or venous vascular origin (Pinotti, 1994).

The low occurrence rate of mesenteric ischemia can be explained by the intense network of anastomoses of the intestinal circulatory system, which ends up irrigating and fulfilling tissue needs. One clear example of this is the low number of cases of gastrointestinal occlusive processes observed in individuals in England, which are approximately 50 times less frequent than cases of acute myocardial infarction (Hohenwalter, 2009; Ward et al., 1995). However, when this clinical condition occurs, it is characterized by abdominal pain, distension of bowel loops and wall thickening, generalized peritonitis, leukocytosis and melena, which can evolve into intestinal necrosis, reaching mortality rates higher than 80% (Chiu et al., 1970).

Although obstructive processes of mesenteric veins may occur in cases of schistosomiasis, considering that this vascular network is the habitat of the parasite, these processes seem not to have an impact on the pathogenesis of the disease. However, this may not occur in the animal model of the disease, in which mice are used as definitive parasite hosts in laboratory infections.

This suspicion arose owing to the death, due to mesenteric ischemia, of a mouse infected by *S. mansoni* in the vivarium of the Aggeu Magalhães Institute (IAM-FIOCRUZ). In addition to this, records of high mortality rates among the infected animals triggered the need to investigate and identify what the main cause of death among these animals was.

## MATERIAL AND METHODS

The present study was approved by the Animal Ethics Committee of the Aggeu Magalhães Institute (CEUA/IAM), under approval certificate no. 48/2013. To maintain the biological cycle of *S. mansoni*, the Schistosomiasis Laboratory and Reference Service (RSS) of IAM-FIOCRUZ percutaneously infects male and female outbred Swiss Webster mice every month, with 120 cercariae of the BH and LE lineages in the proportions of 20 animals per strain. These animals are used for the obtention of miracidia from their faeces to infect *Biomphalaria glabrata* snails and obtain more cercariae to infect other animals and maintain the parasite cycle. In addition, adult worms are obtained to extract DNA to develop a positive control molecular diagnoses by conducting polymerase chain reaction (PCR) analysis. Finally, soluble egg antigen (SEA) and soluble adult worm antigen preparation (SWAP) are produced.

A total of 220 infected animals were studied between October 2016 and May 2017 (110 BH lineage cercariae and 110 LE lineage cercariae). According to the rules established in the standard operational procedure (SOP), of the RSS, six months after the animals are infected or if, at any time during this period, they present any indication of distress as a result of the infection, they should be euthanized. Every animal that died or required euthanasia was necropsied; in addition, adult worms were collected and counted. The necropsy procedure consisted of making a sagital incision in the animals' abdomen to expose abdominal viscera.

Fragments from their intestines, mesenteric vessels and livers were removed immediately after death and were subjected to histopathological and morphometric analyses. Three fragments of liver tissue in transverse sections were collected from each animal. Horizontal histological sections (5 μm) were cut using a microtome *Leica RM2235* and the slides were stained with hematoxylin-eosin and Masson trichrome for morphometric study. The study was performed using ImageJ Software (National Institutes of Health, USA) for measuring the average diameter (micrometer - μm) of granulomas, with subsequent calculation of the area ($\mu m^2$) and intensity of the blue stain (specific for collagen) in histograms. The number of inflammatory cells in the granulomas was analyzed using a Nikon Eclipse E200 microscope which was used at 10x and 40x magnifications on images randomly obtained in 10 fields/animal. The samples were evaluated according to the degree of the lesions in the mucous tunic, in accordance with the modified classification proposed by Chiu et al. (1970); Longo et al. (1992).

Samples were also analyzed according to the acute intestinal ischemia scale, which is characterized by three stages. Stage I is pathologically characterized by necrosis, erosion, ulcerations, edema and hemorrhage located in the mucosa; this stage is still reversible. Stage II comprises necrosis that extends to layers of the submucosa and muscularis propria. Finally, Stage III presents high mortality rates and affects all three layers (Jatobá et al., 2008).

*Table.* Classification of intestinal morphology of mesenteric ischemia.

| Classification modified from Chiu et al., 1970 | |
|---|---|
| Grade 0 | Mucosa without alteration. |
| Grade 1 | Well-constituted villi without cell lysis or inflammatory process, but with formation of Gruenhagen subepithelial space. |
| Grade 2 | Presence of cell lysis, formation of Gruenhagen subepithelial space and thickening between villi. |
| Grade 3 | Destruction of free portion of villi and presence of dilated capillaries and inflammatory cells. |
| Grade 4 | Structural destruction of villi, with the presence of only the framework of some of them, formed by inflammatory cells and necrotic material, with hemorrhage and basal glandular ulceration. |
| Grade 5 | Destruction of the entire mucous tunic, where glandular structures are no longer observed and only amorphous material is deposited over the submucosal screen. |

Deaths were divided into two classes: due to mesenteric ischemia, when macroscopic signs of necrosis in parts of the intestine were identified; and due to unknown cause, when no clinical and/or macroscopic signs of the cause of death were present or when the state of the tissues did not allow identification of the cause of death. Feces were collected and analyzed by reaction to hydrogen peroxide, based on the protocol used by Jatobá et al. (2008) in order to investigate occult blood in fecal matter (Lins et al., 2008).

The date of death and infection, *S. mansoni* strain lineage, and cause of death were recorded for all animals that died. The Kaplan-Meier estimator was used to analyze the deaths in the present study and to compare them to the deaths of inbred BALB/c mice with high parasitic loads (80 cercariae) and low parasitic loads (30 cercariae). *Microsoft Excel* 2013 software was used for data tabulation and *GraphPad Prism* V6 (San Diego, CA, USA) for subsequent analyses.

## RESULTS

Over an eight-month period, 70 deaths were recorded and the recovery of worms revealed that the average number of adult couples was 36.6, the highest number was 47 couples and the lowest was 25 couples. There was no statistically significant difference between the various types of death. Three animals presenting altered clinical conditions, were euthanized and the tissues were removed immediately. The remaining 67 animals were found dead. Out of the total number of deaths, 42 animals presented mesenteric ischemia with anatomopathological alterations similar to those shown in Figure 1: macroscopic signs of necrosis in parts of the intestine and feces with positive reaction to hydrogen peroxide.

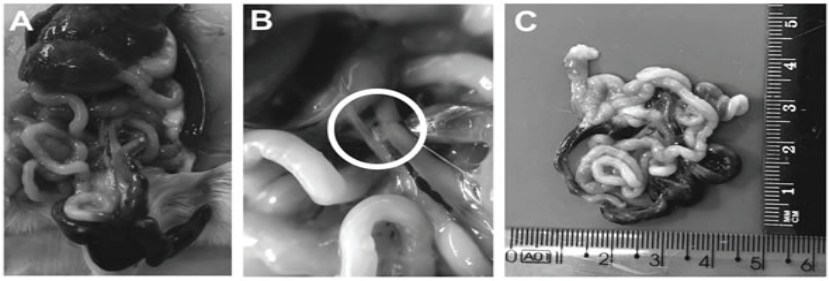


*Figure 1*. A. Obstructed mesenteric vessel with intestinal ischemic area. B. View of worms obstructing a mesenteric vessel. C. Intestine with irrigated and ischemic area.

A Kaplan-Meier estimate is illustrated in Figure 2. The present data regarding animal survival analysis indicated that the percentage of deaths due to mesenteric ischemia was 35.9%. Compared with the percentage of deaths from unknown causes in Figure 2A, an increase of approximately 10% was noted for mesenteric ischemia. Deaths began to occur between 31 and 60 days after infection and most of the episodes occurred from 91 to 120 days after infection for mesenteric ischemia, and from 121 to 150 days after infection for unknown causes. Figure 2B shows that the death of animals with a high parasite load begins at about 55 days after infection, an early date when compared to the deaths in animals with low parasite loads which started after 230 days.

The difference between the livers of infected and uninfected animals was easily noted. Figures 3A, C and E show liver tissue integrity and the presence of only a few inflammatory cells. Figures 3B, D and F show the liver damage caused by *S. mansoni* eggs, with a large lesion in hepatocytes. An egg is located at the center of the granuloma, and lymphocytes, macrophages and polymorphonuclear cells (neutrophils and eosinophils) have accumulated around it. It is an exudative-productive granuloma characterized by a rich structure of collagen fibers and inflammatory cells concentrated in the margins, thus showing a more organized and circumferential appearance (as described by Wiesner et al., 2001).

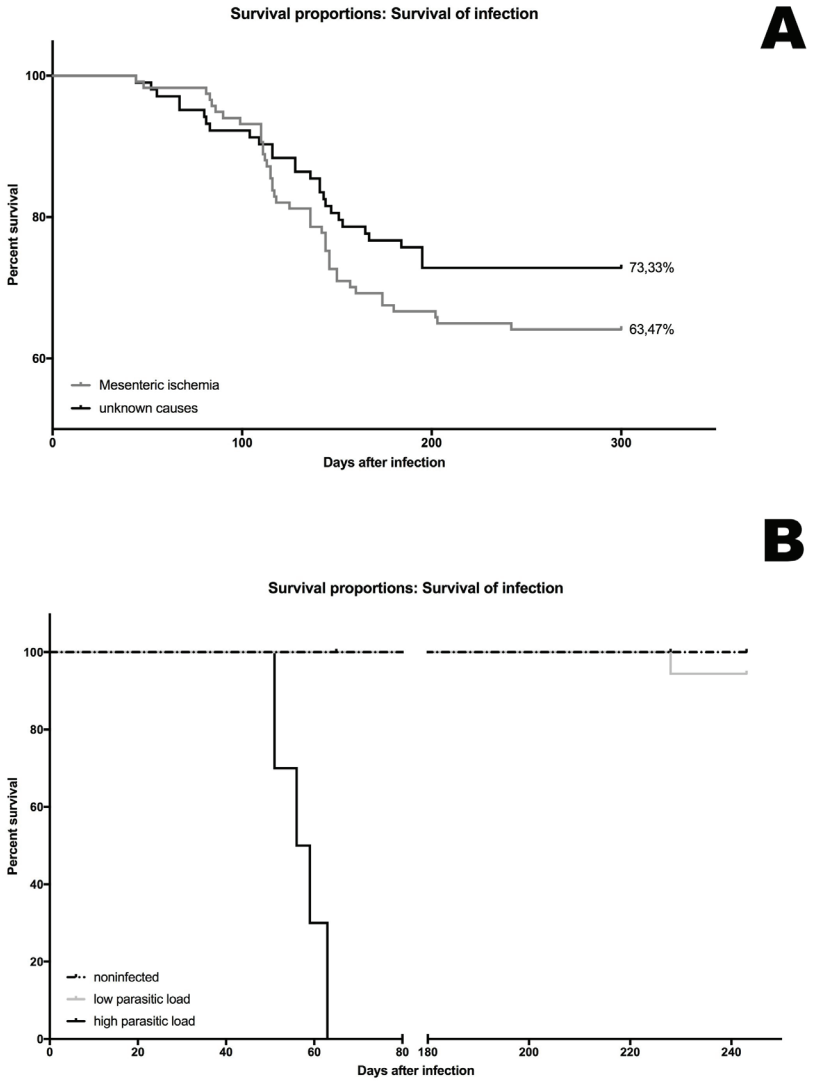


*Figure 2.* Survival curve of *S. mansoni* infection. A: Comparison of deaths due to mesenteric ischemia and unknown causes (120 cercarie) of outbred *Swiss Webster* mice. B: Comparison of deaths with high parasitic load (80 cercariae) and low parasitic load (30 cercariae) of inbred BALB/c.

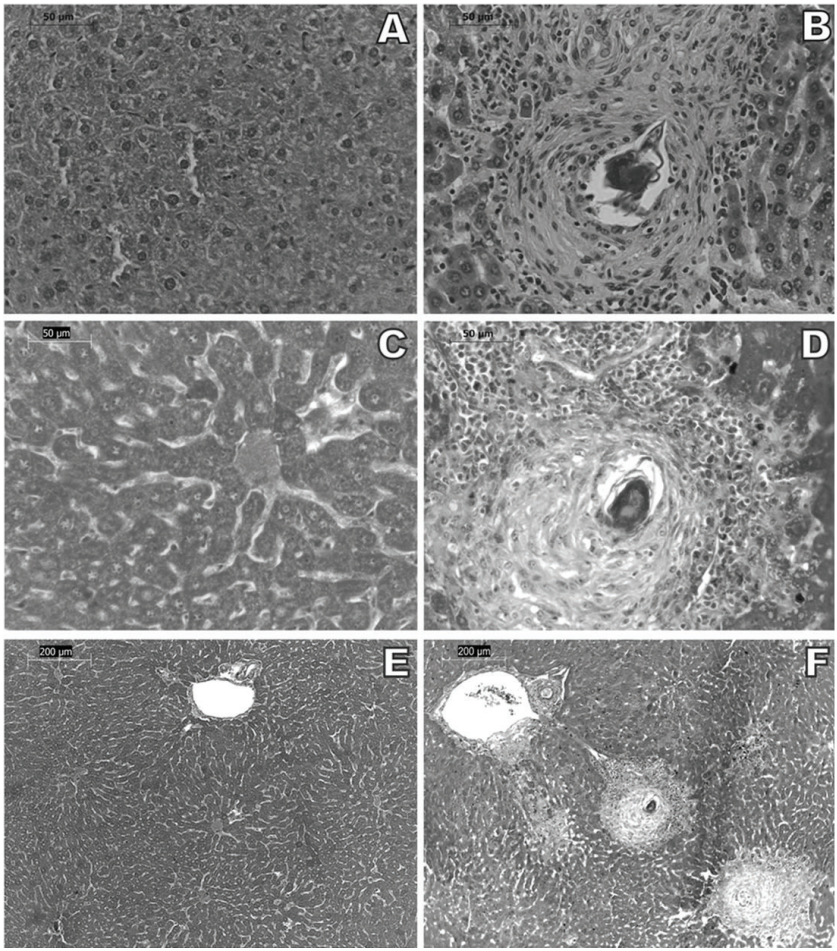


*Figure 3*. Photomicrographs of mouse livers. A, C and E: Liver of an uninfected animal (A: hematoxylin and eosin, scale bar = 50 µm / C: Masson trichrome Scale bar = 50 µm / E: Masson trichrome Scale bar = 200 µm). B, D and F: Liver granuloma presenting a thick band of fibrosis between an egg and the liver tissue of an infected animal that died due to mesenteric ischemia (B: hematoxylin and eosin, scale bar = 50 µm / D: Masson trichrome Scale bar = 50 µm / F: Masson trichrome Scale bar = 200 µm).

Figure 4A shows the presence of an exuberant chronic inflammatory infiltrate and full destruction of the mucosa in the ascending colon of the large intestine. In the submucosal region, multiple malformed granulomas with incipient fibroplasia around *S. mansoni* necrotic eggs and an accumulation of eosinophils can be observed. Occasional hemorrhagic foci and preservation of the muscle layer can be identified.

Figure 4B shows the presence of *S. mansoni* necrotic eggs (star) in the submucosal region of the large intestine surrounded by chronic inflammatory infiltrate with predominance of mononuclear cells and eosinophils (arrow tip). According to Table (page 4), the analysis on Figure 4 indicated a grade 4 mesenteric ischemia lesion characterized by structural destruction of villi, presenting only the framework of a few of these, formed by inflammatory cells and necrotic material, and presenting hemorrhage and basal glandular ulceration. Considering the early deaths of these animals, the samples could also be analyzed using the intestinal acute ischemia scale. The tissue lesions presenting that ischemia were evolutionary stage III, whose main characteristic is to affect all three tissue layers (mucosa, submucosa and muscle).

Figures 4C and D show the intestine of an animal with unknown causes of death, where intestinal damage is due only to the presence of *S. mansoni* eggs. Lastly, figures 4E and F show the intact tissue of a noninfected animal presenting grade 0 according to Table (page 4).

Figure 5 shows photomicrograph of the parasite inside the superior mesenteric vein, with reduction of blood flow and production of an ischemic process. Macroscopically, continuous lesions widely distributed along the ileum, cecum and colon were observed. The affected areas of the intestine were dark red or purple due to luminal hemorrhage. Furthermore, mucosa thickening was noted, caused by hemorrhage and edema. These animals' feces were dark and reacted positively to hydrogen peroxide, thus confirming the presence of blood. Figure 5 highlights an area where the presence of two pairs of *S. mansoni* were observed, blocking the superior mesenteric vein, thereby obstructing blood flow to the intestine.

The morphometric analysis results revealed that livers from animals with mesenteric ischemia presented a higher percentage of collagen, with larger granulomas and, consequently, larger areas than livers from animals that died from unknown causes ($p < 0.05$). However, the number of inflammatory cells in these animals was lower.

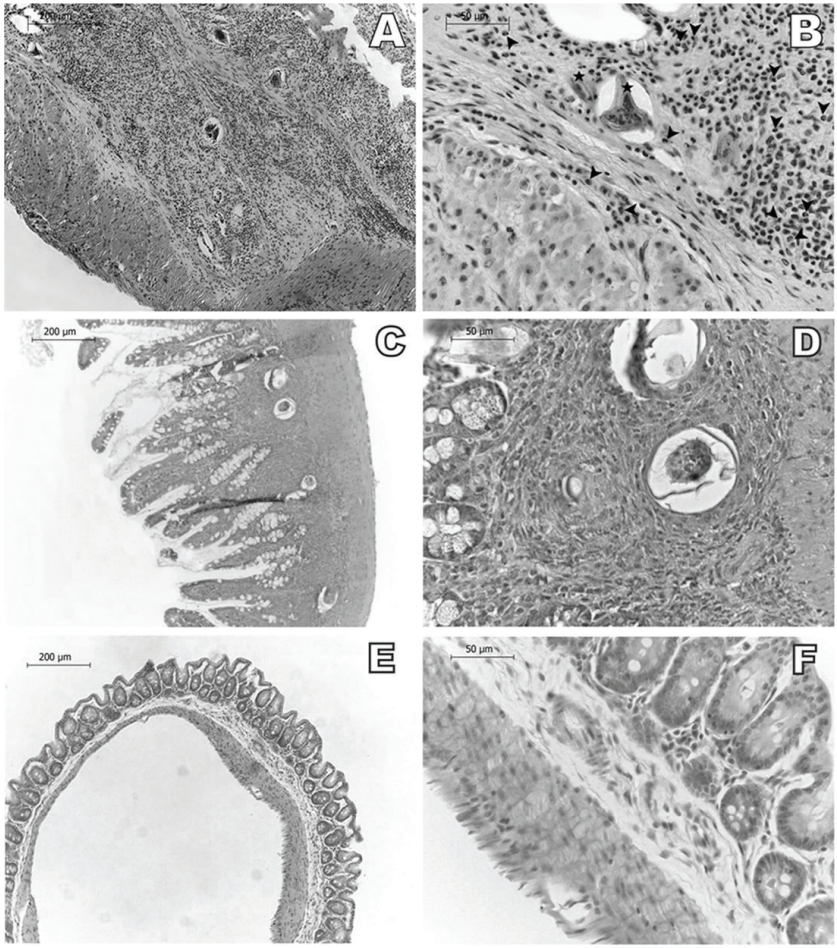


*Figure 4.* Photomicrographs of the region of the ascending colon in the large intestine in an animal with mesenteric ischemia. A. Presence of an inflammatory infiltrate can be observed (hematoxylin and eosin, Scale bar = 200 µm) B. Animal with mesenteric ischemia, *S. mansoni* eggs (*) and chronic inflammatory infiltrate (arrow) (hematoxylin and eosin, Scale bar = 50 µm). C and D: Animal with unknown cause of death, presence of eggs and granuloma (hematoxylin and eosin, C Scale bar = 200 µm and D Scale bar = 50 µm E and F: Noninfected animal (hematoxylin and eosin, E Scale bar = 200 µm, and F Scale bar = 50 µm.

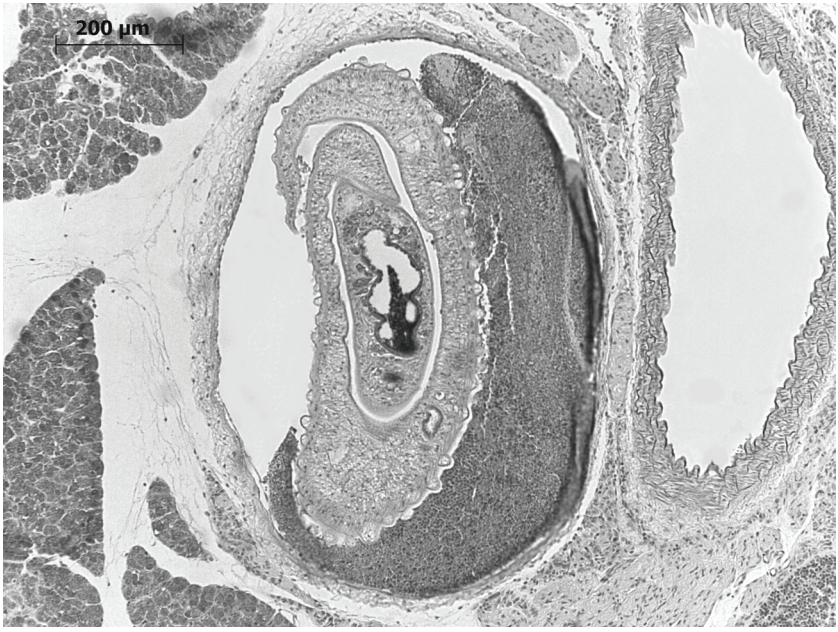


*Figure 5*. Photomicrograph of superior mesenteric vein with an adult *S. mansoni* worm pair inside, stained with hematoxylin and eosin; Scale bar = 200 µm.

## DISCUSSION

In humans, the mechanical occlusion of mesenteric vessels by parasites is rare (Rha et al., 2000); however, in the present study, this was the most common type of impairment, occurring in over 30% of the cases. Figure 2B illustrates this typical presentation of mesenteric ischemia. When the occlusion occurs, the low-pressure venous output is compressed and, consequently, there is loss of arterial input. Strangled intestine segments are usually filled and distended and present edema with ascites (Rosenblum et al., 1997).

The intestinal mucosa has a high metabolism, therefore, requiring high blood perfusion. The ischemia causes rupture of the mucosal barrier, allowing the release of bacteria, toxins and vasoactive mediators, which in turn cause myocardial depression, systemic inflammatory response (sepsis and septic shock), even multiple organ failure and death. The release of mediators may occur even before the complete infarct, and necrosis may occur 10 to 12 hours after symptomatology (Nuzzo et al., 2017; Studer et al., 2015).

The superior mesenteric vessel network provides blood supply for the third and fourth portions of the duodenum through the superior and inferior pancreaticoduodenal arteries, and irrigates the jejunum, ileum and colon at the level of the splenic flexure (Herbert et al., 2004; Lenzi et al., 1998). Figure 2 shows the ileum, cecum and ascending colon darkened due to vessel occlusion and luminal hemorrhage. In humans, approximately 15% of all cases of mesenteric ischemia are due to mesenteric venous thrombosis. The diagnosis is complex, because the abdominal symptoms are nonspecific besides presenting general symptoms such as pain, nausea and vomiting (Bergqvist & Svensson, 2010; Rhee & Gloviczki, 1997).

To what extent do worms disrupt blood flow and lead to an ischemic process? In Figure 5 the worm is observed occluding a large part of the lumen of the vessel with a large thrombus around it, this obstruction induces turbulence in the vein and increases the shear stress along the vessel wall (Stein & Sabbah, 1974). Allied to this, the worm presence in the blood vessel may possibly cause damages to the vascular endothelium. It is known that there is a decrease in nitric oxide (NO) production and expression of endothelial NO synthase that are essential for vessel wall smooth muscle relaxation, increase in blood flow and decrease in blood pressure (Da'dara & Skelly, 2011; Oliveira et al., 2011; Silva et al.,1998). However, the parasite is highly adapted and has developed mechanisms of blood hypo-coagulation, hyper-fibrinolysis mechanisms and manipulation of vascular tone, which enable its survival in the bloodstream of the host (Mebius et al., 2013). This is successfully applied in human infection, where the caliber of the vessels is superior to mice vessels; however, even though the parasite synthesizes substances that avoid the Virchow Triad, the dimensions of the parasite when compared to those of the mesenteric vessels decrease the blood flow partially or totally and lead to ischemic processes.

In the present study, this anatomopathological presentation was more common than expected and, during the study period, mesenteric ischemia was detected as the main cause of death. This cause of death was confirmed to be higher than the unknown causes differently from that noted in humans (Sise, 2014), the hypothesis is that this high number was due to the animal's anatomy itself, which favors the pathological process. Due to the small caliber of the mesenteric vessels in mice, the worms are more likely to block blood vessels and begin an ischemic process. Consequently, the higher the parasitic load, the higher the likelihood of incidents such as these.

The death of animals with mesenteric ischemia and the approximately 10% lower survival number in the group that died from unknown causes hamper maintenance of the artificial cycle of *S. mansoni*, preventing the regular supply of miracidia for infecting mice. This consequently hinders release of cercariae to infect new animals and affects laboratory studies on the disease. More deaths mean less raw material for producing SEA and SWAP antigens and positive controls for PCR. Although The Kaplan-Meier estimate of Figure

2B is with another mouse species, it is clear when comparing the death rate of different parasitic loads. Longer animal survival enables better organization of laboratory routines and schedules. In addition, it also reduces the use of material, financial and human resources. There was no statistically significant difference between the *S. mansoni* BH and LE lineages, thus corroborating the fact that the high death rates occurred due to mechanical obstructive factors, rather than the virulence of the strain.

According to Herbert et al. (2004) and Lenzi et al. (1998), approximately 60% of the eggs produced by *S. mansoni* reach the intestinal lumen and go to the feces; the remaining 40% remain adhered to intestinal mucosa capillaries and liver sinusoids. These eggs release soluble antigens that mobilize macrophages, eosinophils, lymphocytes and plasma cells mediated by TNF, Th1 and Th2 cells and CD8 T lymphocytes. There is an accumulation of cells around eggs, an increase in the number of fibroblasts, production of collagen and, consequently, formation of schistosomal granulomas (Cerqueira et al., 2005). Although eggs can be observed in the intestinal tissue in Figure 4, they are not the cause of the chronic inflammatory infiltrate or the destruction of the organ's tissue structure, nor the cause of death. Animals with histopathological characteristics similar to those seen in Figure 4 died due to the ischemic process, which caused release of lactate and metabolic acidosis and led to a shock condition (Lee & Lee, 2005; Lins et al., 2008).

The analysis of morphometric data showed that animals with mesenteric ischemia apparently presented a more robust collagen structure of granulomas than did the animals with unknown causes of death. However, the small number of animals analyzed did not allow any inference for hypotheses. This difference could have been due to the evolutionary level of the granuloma, which progressively increases its collagen network, or to the immunological situation (Amaral et al., 2017), in which the animals were found, since the species studied (Swiss Webster) is not isogenic.

According to Da Silva (1992), a higher increase in the number of inflammatory cells was noted between 45 and 55 days after infection, and this number significantly decreased after the 55$^{th}$ day (Da Silva, 1992). The histomorphometric findings are not sufficient to allow inferences, and further studies with higher percentages of slides analyzed are expected to be conducted in order to investigate the relationship between early death due to mesenteric ischemia and the evolutionary stage of granulomas.

The present study identified the need to reduce the parasitic infection load from both strains analyzed, in order to increase animal survival and aid the maintenance of the artificial cycle of *S. mansoni*. The importance of intercommunication between vivaria, laboratories and reference services for schistosomiasis is also highlighted. Effective solutions should be studied for reducing the death rates among the animals that maintain the cycle.

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