Life and death at the mucosal-luminal interface: New perspectives on human intestinal ischemia-reperfusion

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• None
Necrotizing enterocolitis (NEC)?
Intestinal ischemia-reperfusion (IR): a life-threatening phenomenon

Mortality remains >60%

Grootjans, Derikx et al. WJG 2016
Factors associated with high mortality of intestinal IR

• Delayed diagnosis
  o Limited non-invasive diagnostic options
  o Early diagnosis reduces mortality by 50%
Factors associated with high mortality of intestinal IR

- Delayed diagnosis
  - Limited non-invasive diagnostic options
  - Early diagnosis reduces mortality by 50%

- No preventive/therapeutic strategies
  - Limited knowledge on the pathophysiology of human intestinal IR
General aims of the project

New insights in human intestinal ischemia-reperfusion

- To facilitate early diagnosis of intestinal IR
- To elucidate the pathophysiology of human intestinal IR
General aims of the project

New insights in human intestinal ischemia-reperfusion

- To facilitate early diagnosis of intestinal IR
- To elucidate the pathophysiology of human intestinal IR
Pathophysiology: mainly animal studies

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<tbody>
<tr>
<td>0. Normal mucosa</td>
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<tr>
<td>1. Subepithelial space at villus tips</td>
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<tr>
<td>2. Extension of subepithelial space</td>
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<td>with moderate lifting</td>
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<td>3. Massive lifting down sides of villi,</td>
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<tr>
<td>some denuded tips</td>
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<td>4. Denuded villi, dilated capillaries</td>
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<td>5. Disintegration of lamina propria</td>
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<th>Park</th>
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<td>6. Crypt layer injury</td>
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<td>7. Transmucosal infarction</td>
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<tr>
<td>8. Transmural infarction</td>
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</tbody>
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New model to study intestinal ischemia in man

Derikx et al. Plos One 2008
Short period of ischemia leads to reversible damage.

Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011
Short period of ischemia leads to apoptosis of mature enterocytes

Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011
Short period of ischemia leads to reversible damage.

Control | 30I | 30I 30R | 30I 120R

Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011
Zipper-like constriction

Derikx et al. Plos One 2008
Grootjans, Derikx et al. J Pathol 2011
Short period of ischemia does **not** lead to inflammation

Matthijsen, Derikx et al. Plos One 2008
Short period of ischemia leads to reversible functional damage

Schellekens, Derikx et al. WJG 2017
Long period of ischemia leads to irreversible damage

Grootjans, Derikx et al. Gastroenterology 2011
Long period of ischemia leads to inflammation

Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016
Long period of ischemia leads to inflammation and Paneth cell apoptosis

Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016
Long period of ischemia leads to Paneth cell apoptosis and ER Stress

Grootjans, Derikx et al. Gastroenterology 2011
Grootjans, Derikx et al. WJG 2016
Long period of ischemia leads to Paneth cell apoptosis and ER Stress
New model to study colon ischemia in man

Grootjans et al. Gut 2013
Short and long periods of colon ischemia lead to reversible damage

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<th>60I 60R</th>
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Grootjans et al. Gut 2013
Compound exocytosis

Grootjans et al. Gut 2013
Short and long periods of colon ischemia do not lead to inflammation

1. What causes the sequelae of intestinal ischemia?
2. How to prevent it?
Role of proteases: normal intestine
Role of proteases:
intestinal ischemia

(A) Control Small Intestine

Pancreatic Digestive Enzymes

Venule

Lymphatic Duct

Mucosal Barrier

Tunica Serosa

(B) Ischemic Small Intestine

Elevated Permeability of Mucosal Barrier
Role of proteases: autodigestion
Trypsin activity is increased after long period of jejunal ischemia.
Proteases are crucial during intestinal ischemia in animals.
Proteases are crucial during intestinal ischemia in animals.
Protease inhibition leads to less mucosal cell damage in long jejunal IR.
Protease inhibition leads to less mucosal cell damage in long jejunal IR.
Protease inhibition leads to less mucosal cell damage in long jejunal IR
Protease inhibition leads to less inflammation in long jejunal IR
Conclusion

• Short jejunal ischemia leads to reversible damage
  ➔ zipper-like constriction

• Long jejunal ischemia leads to irreversible damage
  ➔ Paneth cell apoptosis

• Long colon ischemia leads to reversible damage
  ➔ compound exocytosis mucus

• The role of proteases as mediators of autodigestion
Thank you…

Wim Buurman
Dirk Schellekens
Inca Hundscheid
Claire Leenarts
Kaatje Lenaerts
Joep Grootjans
Kees de Jong
Thank you for your attention

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Protective mechanisms