Gut Ischemia-Reperfusion Produces Lung Injury via a Mechanism Which Involves Xanthine Oxidase and Phospholipase A2

Kaoru Koike and Ernest E. Moore

ABSTRACT
The gut and the neutrophil (PMN) have been emphasized to play mechanistic roles in the development of adult respiratory distress syndrome and multiple organ failure. Reactive oxygen metabolites and various lipid mediators have been implicated as key players in these pathophysiology. We have previously shown that gut ischemia/reperfusion (I/R) provokes neutrophil-mediated lung injury. We hypothesized in this study that gut I/R produces lung injury via a mechanism which involves xanthine oxidase (XO) and phospholipase A2 (PLA2). Methods: Sprague-Dawley rats were divided into five groups. 1) Normal rats, 2) I/R group: Rats were subjected to 45 min of superior mesenteric artery (SMA) occlusion, 3) Sham-laparotomy group (Lap): Rats underwent the same procedures except SMA occlusion, 4) XO-inactivated I/R group (Tung+I/R): Rats were fed tungsten enriched, molybdenum depleted diet for three weeks to inactivate XO before SMA clamp, 5) PLA2-inactivated I/R group (Quin+I/R): Rats were pretreated with a PLA2 inhibitor, quinacrine (10 mg/kg, IV), prior to the induction of gut ischemia. Six hr after reperfusion, circulating PMN priming was determined by the difference in superoxide generation with and without the activating stimulus, N-formyl-Met-Leu-Phe (fMLP). Pulmonary PMN sequestration was quantitated by myeloperoxidase (MPO) activity, while lung endothelial permeability was assessed by 125I albumin lung/blood ratio. Results: Gut I/R markedly enhanced PMN superoxide production in the presence of fMLP, increased pulmonary MPO activities, and provoked 125I albumin lung leak. Although the Tung+I/R and Quin+I/R groups did not alter I/R-induced pulmonary MPO activities, these groups attenuated gut I/R-induced circulating PMN priming and abrogated gut I/R-induced lung injury. Conclusion: These data suggest that both XO and PLA2 activation are proximal steps in the pathogenesis of lung injury following splanchnic hypoperfusion.

Key Words: multiple organ failure, adult respiratory distress syndrome, neutrophil, priming, small intestine

INTRODUCTION
Gut ischemia/reperfusion (I/R) has been implicated as the central event initiating postinjury multiple organ failure (MOF). We have previously shown that gut I/R produces lung injury by a mechanism that involves neutrophil (PMN) priming1-6. Xanthine oxidase (XO) is an important source of oxygen-centered free radicals in biologic systems and the gut mucosa has a tremendous amount of this enzyme in both endothelial and epithelial cells7. The concept that XO-derived oxidants mediate gut I/R-induced local injury was first proposed in 19818 and was further tested in other organ systems. Phospholipase A2 (PLA2), a ubiquitous cellular membrane enzyme, has been found highly concentrated in gut mucosa9,10 and the activation of this enzyme also appears to be a pivotal
step in the pathogenesis of local injury following gut I/R. Our study hypothesis is, therefore, gut I/R promotes distant organ injury by serving as a priming bed for circulating PMNs that is dependent on XO and PLA₂ activation.

**MATERIALS AND METHODS**

**Gut I/R model.** Adult male Sprague–Dawley rats (Sasco Inc. Omaha, NE) were housed in an authorized facility at Denver General Hospital, and all animal studies were approved in advance by the Institutional Animal Care and Use Committee. Rats weighing 300 to 350 gm were maintained at 25°C, fed rat chow (Agway Prolab 3000, Denver, CO) given water ad libitum, and subjected to 12 hr light–dark cycles. Operative procedures were performed under general anesthesia induced by ketamine 80 mg/kg (Parke–Davis, Morris Plains, NJ) and xylazine 8 mg/kg (Mobay Corporation, Shawnee, KS). Following a midline laparotomy incision, the superior mesenteric artery (SMA) was isolated and occluded with a bulldog arterial clamp applied at the aortic origin. The abdomen was then covered with a sterile plastic wrap. After 45 min of intestinal ischemia, the arterial clamp was removed, the laparotomy incision closed, and animals allowed to wake. Six hr after reperfusion, circulating neutrophil priming, lung neutrophil presence and pulmonary microvascular permeability were quantitated. Forty-five min of clamp time was based on preliminary work demonstrating this relatively brief period of ischemia resulted in 100% survival and did not alter intestinal mucosa by histologic examination at 24 hr reperfusion.

**XO inactivation.** XO inactivated rats were fed tungsten enriched, molybdenum depleted diet (0.7 mg Na tungstate/kg chow, ICN Biochemicals, Cleveland, OH) for 3 weeks before study. This regimen leads to incorporation of tungsten, rather than molybdenum, into XO and thereby inactivates it. The tungsten–supplemented diet has been shown to reduce more than 75% of intestinal mucosal XO activity.

**PLA₂ inactivation.** To study the impact of PLA₂ inhibition, quinacrine (10 mg/kg, dissolved in 500 µl saline) was delivered intravenously prior to the application of the SMA clamp. This pretreatment with quinacrine has been shown to prevent the increase in gut PLA₂ activity after ischemia. Quinacrine (mepacrine) is a synthetic acridine derivative, structurally related to primaquine, and employed clinically as an antimalarial agent. The mechanism of antimalarial activity is not known, but quinacrine is believed to inhibit PLA₂ by altering substrate–enzyme interaction.

**Experimental design.** Rats were divided into five study groups. Sham–operated laparotomy animals were submitted to all procedures except SMA occlusion. The study groups, therefore, included 1) Normal, 2) Sham–Laparotomy, 2) Gut I/R, 3) Tungsten + I/R, and 4) Quinacrine+I/R. Each group has more than five animals.

**Circulating neutrophil priming for superoxide production.** After 6 hr reperfusion, blood was collected from the inferior vena cava, 8 ml per animal, and mixed with 0.8 ml of 3.8% sodium citrate in 15 ml polypropylene tubes. The blood was centrifuged at ×514 g for 22 min at ambient temperature. Plasma was then removed and mixed with 5 ml of 6% dextran and sufficient saline to reach a volume of 14.5 ml. After 30 min sedimentation, the upper cell–free layer was removed, and the cells were washed and resuspended in 2 ml heat–inactivated fetal calf serum (FCS). The cell suspension was underlaid with 2 ml 42% Percoll and then 2 ml 51% Percoll, and the discontinuous Percoll gradient centrifuged at 228 g for 12 min. The neutrophils were collected at the interface of 42%–51% Percoll layers, washed twice in phosphate buffered salt (PBS) containing 0.1% dextrose, and resuspended for assay. The recovery rate of neutrophils was >95% and cell viability, assessed by trypan blue exclusion, was >99%.

Superoxide (O₂⁻) production was measured by superoxide dismutase (SOD)–inhibitable cytochrome C reduction in a 96–well flat bottom culture
plate. Each well contained 75 μM cytochrome C, 15 μM SOD and 2 × 10⁵ neutrophils. Neutrophil priming was determined by measuring superoxide generation in response to the activating stimulus N-formyl-methionyl-leucyl-phenylalanine (fMLP, 10⁻⁶ M). This dose of fMLP did not induce superoxide generation in quiescent neutrophils. The optical density of the wells was measured immediately after the addition of fMLP and monitored every 20 seconds at 550 nm and 450 nm for 5 min. Vmax was determined from the first 5 data points using Softmax (Molecular Devices, Menlo Park; CA).

**Lung preparation.** The animals were reanesthetized at 5.5 hr reperfusion, and 1.0 μCi ¹²⁵I-labeled bovine albumin (ICN Radiochemicals, Irvine, CA) in 0.5 ml of PBS injected into the inferior vena cava. Blood and lung were sampled 30 min later. For lung harvest, a tracheostomy was performed and the animals ventilated with room air plus 5% CO₂ at 60 breaths/min, 9 cm H₂O peak inspiratory pressure, and 2 cm PEEP. A median sternotomy was performed and 1.0 ml of heparinized blood obtained from the ascending aorta. Lungs were heparinized (500 U) via the right ventricle and perfused with modified Krebs-Henseleit solution (pH 7.4, 37°C, containing 4 gm% Ficoll 70 and 10 mM N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid) at 0.04 ml/gm body wt/min. The left lung was then exised, rinsed externally with saline, blotted dry, and weighed.

**Lung myeloperoxidase assay.** Myeloperoxidase activity was measured as an index of neutrophil presence. Perfused lung samples, 400 to 600 mg, were homogenated for 30 sec in 4 ml of 20 mM potassium phosphate buffer, pH 7.4, and centrifuged for 30 min at 40,000 g, 4°C. The pellet was resuspended in 4 ml of 50 mM potassium phosphate buffer, pH 6.0, containing 0.5 gm/dl hexadecyltrimethyl ammonium bromide, and sonicated for 90 sec. Samples were incubated at 60°C for 2 hr and centrifuged. The supernatant, 0.1 ml, was added to 2.9 ml of 50 mM potassium phosphate buffer, pH 6.0, containing 0.167 mg/ml O-dianisidine with 0.0005% hydrogen peroxide, and absorbance of 460 nm visible light (A₄₆₀) measured for 3 min (Beckman DU7 spectrophotometer, Irvine, CA). Myeloperoxidase activity (units/gm) = ΔA₄₆₀ × 13.5/gm, where ΔA₄₆₀ = rate of change in absorbance between 1 and 3 min.

**Lung ¹²⁵I albumin leak.** The left lung and 1.0 ml blood were counted for ¹²⁵I radioactivity (Packard 5330 Scintillation Spectrometer, Downers Grove, IL). Lung protein flux, as reflected by ¹²⁵I albumin lung uptake, was calculated as the ratio of ¹²⁵I lung counts to ¹²⁵I blood counts.

**Statistics.** Data variables are reported as mean ± standard error of the mean (SEM). The data in each study group were subjected to one-way analysis of variance (ANOVA) followed by Scheffe F-test for group pairs. P values of <0.05 were considered significantly different.

**RESULTS**

**Circulating neutrophil priming.** Neutrophils isolated from normal laboratory animals had no measurable basal O₂⁻ production (Fig. 1) and responded minimally to fMLP (7.0 ± 0.5 nmol O₂⁻/10⁶ cells/min). Basal rate of neutrophil superoxide production from sham–laparotomy animals was 2.3 ± 1.5 nmol O₂⁻/10⁶ cells/min which increased to 18.1 ± 7.8 nmol O₂⁻/10⁶ cells/min with fMLP. Basal superoxide production from neutrophils harvested from gut I/R animals at 6 hr reperfusion was 7.1 ± 3.5 nmol O₂⁻/10⁶ cells/min, but increased dramatically (p < 0.05) in response to fMLP (44.9 ± 8.9 nmol O₂⁻/10⁶ cells/min). In contrast, gut I/R animals fed tungsten had attenuated O₂⁻ release without (7.6 ± 0.7) or with fMLP (21.7 ± 3.1) which was similar to the laparotomy alone group, while gut I/R animals pretreated with quinacrine had the least O₂⁻ generation without (0.6 ± 0.6) or with fMLP (2.4 ± 1.6).

**Lung myeloperoxidase activity.** Normal lung myeloperoxidase level was 2.4 ± 0.3 units/gm (Fig. 2). With laparotomy this increased to 11.9 ± 0.4 units/gm (p < 0.05). Lung myeloperoxidase level in
Superoxide production of circulating neutrophils at 6 hr of reperfusion obtained from: 1) normal (NL), 2) sham-laparotomy (Lap), 3) 45 min of gut ischemia followed by 6 hr reperfusion (I/R), 4) I/R after tungsten diet (Tg+I/R), and 5) I/R with quinacrine pretreatment (Quin+I/R). The neutrophils were exposed to buffer alone (−fMLP; ≪) or 10^-6 M fMLP (+fMLP; ≡). * p<0.05, compared to the other groups.

Gut I/R animals was 13.6±1.1 units/gm, significantly different from normal control (p<0.05) but not from laparotomy. Either tungsten diet or quinacrine pretreatment did not reduce pulmonary neutrophil sequestration following I/R (13.3±1.1, 15.0±0.8, respectively).

Lung 125I-labeled albumin leak. The 125I albumin lung/blood ratio for normal animals was 0.038±0.003 (Fig. 3), and was 0.045±0.004 at 6 hr after laparotomy. Gut I/R increased this ratio significantly to 0.078±0.006 (p<0.05). This microvascular leak at 6 hr reperfusion was ablated in the gut I/R animals pretreated with tungsten or quinacrine (0.024±0.004, 0.034±0.006, respectively).

DISCUSSION

Gut I/R leads to an acute local inflammatory response resulting in an increased microvascular permeability. It has been clearly demonstrated that XO-derived oxidants play an important role in generating gut I/R-induced intestinal microvascular injury. During the ischemic period, ATP is catabolized to yield hypoxanthine. The hypoxic stress also triggers the conversion of xanthine dehydrogenase (XD) to the oxygen radical-producing XO. During reperfusion, molecular oxygen is reintroduced into the tissue where it reacts with hypoxanthine and XO to produce a burst of superoxide anion and hydrogen peroxide. In the presence of iron, superoxide anion and hydrogen peroxide react...
via the Haber–Weiss reaction to form hydroxyl radicals. This highly reactive and cytotoxic radical then initiates lipid peroxidation of cell membrane components and the subsequent release of substances that attract, activate, and promote the adherence of granulocytes to microvascular endothelium. The adherence of granulocytes then cause further endothelial cell injury via the release of superoxide and various proteases.

Recently, major degrees of reperfusion injury in gut mucosa have been shown to occur from mechanisms other than oxygen radicals and lipid peroxidation, and PLA₂ and various PLA₂-dependent compounds, e.g., arachidonic acid metabolites, lysophosphatidyl choline, and platelet activating factor (PAF), have been postulated being involved in this process¹. PLA₂ is a family of sn-2 acylhydrolases that are involved in a number of inflammatory processes. Activated PLA₂ cleaves the sn-2 acyl bond of phospholipids yielding equimolar amounts of free fatty acid and lysophospholipids. Free fatty acid in the form of arachidonic acid serves as a primary substrate for eicosanoids; while lysophospholipids are directly cytotoxic and remodeled to yield PAF.

Gut I/R, as well as other tissue I/R and thermal injury, also causes remote organ dysfunction⁵,⁶. We have previously shown that gut I/R–induced lung injury is accompanied by neutrophil accumulation in the lung²⁴, and either neutrophil–depletion⁸ or blockade of the CD11b/CD18 adhesion receptor on neutrophils eliminates this phenomenon⁹, indicating pathologic neutrophil and vascular endothelial cell interaction presumably promotes destruction of capillary vascular patency and provokes increased tissue permeability. Neutrophil–mediated tissue injury is defined by a sequence of events including neutrophil adherence, diapedesis, and release of neutrophil–generated products. However, neutrophil sequestration is not invariably associated with tissue injury. In fact, a variety of minor insults (e.g., laparotomy alone, placement of intravascular catheters, or injection of a low dose of endotoxin) have been shown to sequester neutrophils in the lung without provoking lung injury⁷,¹⁸. We observed in this study that XO inactivation and PLA₂ inhibition did not attenuate gut I/R–induced pulmonary neutrophil sequestration, but did prevent lung injury. These findings also support the idea that neutrophil adherence to endothelium is a necessary step but not sufficient to produce lung injury.

Instead, neutrophil priming and activation sequences appear to be important cellular processes to generate neutrophil–mediated tissue injury⁶. A conspicuous mechanism through which neutrophils produce tissue injury is the stimulated elaboration and release of reactive oxygen metabolites. Several chemoattractants, such as fMLP, complement derived C5a, leukotriene B₄, interleukine–8, and PAF, are thought to prime neutrophils for the respiratory burst¹⁹. Neutrophil O₂⁻ generation is believed to occur via the NADPH oxidase system, but the precise signalling pathways and secondary events involved in priming and activation remain ill-defined. Activation of protein kinase C appears important for neutrophil priming²⁰.

In the current study, XO inactivation prevented gut I/R–induced neutrophil priming. Priming of the neutrophil may be augmented by direct neutrophil interaction with the injured gut or associated inflammatory mediators released by the I/R process. In our gut I/R model, we noted that circulating neutrophils become primed at 2 hr reperfusion⁴. Pursuing our hypothesis that priming occurred in the intestinal circulation, we determined neutrophil priming at 90 min reperfusion in the mesenteric inflow (aorta=SMA) and compared it to the neutrophil primed state in the mesenteric outflow (portal vein)²¹. At this time point, there was significant priming among the neutrophils exiting the gut contrasted to no evidence of priming at entry. In sum, neutrophil priming in the reperfused gut preceded systemic priming, indicating the gut, following I/R, acted as a priming bed for circulating neutrophils. It is, therefore, conceivable that XO inactivation inhibits neutrophil priming by blocking this process. Recent-
ly, XO has been identified in murine neutrophils but it has not been established that this XO contributes substantially to neutrophil superoxide production\(^{22}\). Specifically, Jones et al have shown that allopurinol failed to block neutrophil respiratory burst in response to zymosan\(^{23}\). The finding in this current study that XO inactivation did not completely eliminate gut I/R-induced neutrophil priming but reduced it to the level seen in the sham laparotomy animals may support this concept. Another possibility to explain the efficacy of XO inactivation in preventing gut I/R-induced lung injury is that tungsten diet attenuated XO activity in the lung. Toxic oxygen metabolites generated by pulmonary XO are responsible for the lung I/R-induced local injury\(^{24}\). We noticed that rats fed a tungsten diet had a 90% decrease in pulmonary XO activity as compared to rats fed a standard diet (unshown data). However, Terada et al have shown that gut I/R does not alter pulmonary XO or XD activity\(^{25}\). Although it is quite difficult to isolate and analyze the action of pulmonary XO in this in vivo system, pulmonary XO may not play a major role in the pathogenesis of gut I/R-induced lung injury.

We also found in this study that PLA\(_2\) inhibition prevented gut I/R-induced neutrophil priming. The products derived from cell membrane phospholipids through PLA\(_2\) activation (e.g., PAF, leukotriene B\(_4\)) are recognized as neutrophil primers\(^{26,27}\). Significant PAF levels were found both in gut mucosa and in the circulation within 15 minutes of gut reperfusion\(^{28,29}\). Increased leukotriene B\(_4\) concentrations were observed in interstitial fluid after less than 10 minutes of gut ischemia\(^{30}\). We examined gut supernatant following I/R and confirmed PAF production in the distal small bowel\(^{31}\). Additionally, a PAF antagonist (WEB2170) inhibited neutrophil priming induced by this gut supernatant. Furthermore, we observed in the gut I/R model that gut PLA\(_2\) activation preceded neutrophil priming and lung leak\(^6\). Taken together, gut PLA\(_2\) activation appears to be a proximal step in the process of gut I/R-induced distant organ injury. The details of PLA\(_2\) activation remain unclear but the accumulation of cytosolic Ca\(^{2+}\) during ischemia could be a mechanism\(^{32}\). Serotonin, thrombin and bradykinin produced during ischemia, are also proposed to stimulate PLA\(_2\) through receptor-operated pathways\(^{33,34}\). Reperfusion may further sustain or augment this PLA\(_2\) activity through reactive oxygen metabolites generated after reoxygenation\(^{35}\). PLA\(_2\) is an ubiquitous enzyme existing in the whole body. neutrophils contain PLA\(_2\) but the dose of quinacrine infused in our model did not suppress the superoxide production capacity within this experimental period\(^{6}\). Pulmonary PLA\(_2\) appears to be not involved in this process, because pulmonary PLA\(_2\) activity could not be detected either in the normal or experimental animals by our hands (unshown data). Our future work will focus on how neutrophil-endothelial cell interaction affects neutrophil priming and activation and how various circulating mediators may modulate this inflammatory process.

**CONCLUSION**

Gut I/R appears to promote lung injury by serving as a priming bed for circulating PMNs via XO and PLA\(_2\) dependent mechanisms. Further elucidation of the pathways regulating PMN priming for cytotoxicity and adhesion to endothelium, and their interaction with cytokines and other inflammatory mediators, may provide new therapeutic targets for reducing the risk of post–injury MOF.

**REFERENCES**

4) Koike K, Moore EE, Moore FA, et al: Gut is-


DISCUSSION

著者は本雑誌、7巻1号に小腸の虚血・再灌流（以下I/R）に伴う障害には好中球のプライミング作用が関与していることを発表されております。今回は小腸I/Rによる障害には腸管粘膜の粘膜性障害が関与していることを、我々の活性物質細胞の実験系でクリアカットに示しております。そこで以下の4点につき、御教示下さい。

1. 共同研究者のDr. Mooreは外傷後の脳器障害に関してtwo hit theoryを提唱されておりますが、著者は好中球のプライミングから障害に至る過程で、second hitに相当するものとしてどういったものと考えておりますか。

2. 本実験系においてプライミングされた好中球の寿命は、いったいどのくらいなのでしょうか。

3. プライミングされた好中球のtarget organとして肺を取り上げておられますか、肝、腎に対する影響はどうなのでしょうか。

4. xanthine oxidaseおよびphospholipase A2が豊富な腸管は、好中球プライミングの場として特異的臓器なのでしょうか。

（東京女子医科大学救急医学 石川 雅健）

1. 外傷患者における検査、受傷後3時間で好中球がhypersensitivityとなって好中球依存性の臓器障害が起こりやすくなり、この状態は12-24時間続くとされています。一方、それ以降では好中球はhyporesponsiveになるために感染症にかかりやすい状態になります。今回報告した動物実験では、小腸虚血・再灌流でプライミングを受けた循環血液中の好中球は腸管小循環内の内皮細胞と相互作用を起こし、肺血管の透過性の亢進を来すものと考えています。われわれは以前、この動物モデルにおける再灌流2時間後に比較的無害なエンドトキシンを腹腔内に投与すると、組織学的にも非常に高度な障害が惹起されることを確認しました。

2. われわれは小腸虚血・再灌流が障害を来す過程をより詳細に検討するために、好中球のプライミングと障害の発生を経時的に調べましたが、それによる結果、好中球のプライミングは再灌流1時間で明らかとなり、6時間でピークに達し、一方、障害は再灌流2時間で出現することを知りました。しかし、それ以降の好中球のプライミングがどのように変化するか、残念ながら調べていません。障害は再灌流18時間で認められなくなることから、好中球のプライミング状態はそれまでに消失するものと想像しています。

3. 小腸虚血・再灌流に伴い、肝臓中心のどのような障害が出現するかを検討すると、再灌流6時間後にはGOT・GPTの上昇、胆汁流出量の減少が認められました。腎障害が出現するかどうかは血中にクレアチニンの変化で調べましたが、コントロールグループとの間に差を認めることができませんでした。血中クレアチニン価の測定では軽微な障害を検出できないか、あるいは実際に腎障害は出現しない、もしくはもっと後期に障害が明らかになるのかは不明です。

4. xanthine oxidaseやphospholipase A2は小腸に豊富に含まれていますが、他の臓器を含む広範な臓器に分布しています。われわれは、小腸が免疫学的には細胞内にactiveで、多臓器不全発生のマーカーであるといわれていることから、小腸虚血・再灌流モデルを用いて遠隔臓器障害発生のメカニズムを検討していますが、肝臓、肺、筋肉組織の虚血・再灌流でも遠隔臓器障害が引き起こされることがわかっています。これらの障害は少なくとも部分的には好中球依存性であることから、好中球のプライミングが臓器以外の臓器で起きる可能性があるでしょう。しかし、これらのモデルにおける好中球のプライミングに関する研究は、いままでなされていません。
小腸虚血・再灌流による肺障害
—キサンチンオキシダーゼとホスピラーゼ A,の役割—

小池 薫¹  Ernst E. Moore²

要旨 好中球は外傷性ショックに続発する成人型呼吸促進症候群や多臓器不全の発症に深く関与している。われわれは以前、小腸虚血・再灌流(ischemia/reperfusion；I/R)は好中球依存性肺障害を惹起することを報告した。本研究では、この病態の発生メカニズムにおいてキサンチンオキシダーゼ(XO)とホスピラーゼ A, (PLA,)がどのような役割を果たしているかを検討した。方法：S-D ラット(オス, 300-350gm)を、以下の 5 つのグループに分けて実験を行った。1) 正常ラット。2) I/R：上腸間膜動脈を 45 分間血行遮断後、血行再開した。3) Laparotomy グループ(Lap)：I/R 以外のすべての処置を行った。4) テングステン(Tg)が豊富で、マリブンを含まない飼料を 3 週間投与したラット(XO 不活化ラット)に、I/R を行ったグループ(Tg+I/R)。5) キナクリン(PLA, 阻害剤：Quin, 10mg/kg, iv)を実験直前に投与し、I/R を行ったグループ(Quin+I/R)。6 時間の再灌流後、血液と肺を採取し、好中球のプライミング(iMLP によるスーパーオキサイド産生量), 肺内好中球数(ミエロペロキシダーゼ活性), 肺障害(125I-アルプミン肺/血液比)を測定した(ANOVA, p<0.05, n≧5)。結果：I/R は好中球のプライミングと好中球の肺内集積を引き起こし、肺障害を惹起したが、Lap は肺内好中球数のみ上昇させた。Lap, I/R グループと、Tg+I/R, Quin+I/R グループとの間に肺ミエロペロキシダーゼ活性値有意差はなかったが、I/R による好中球のプライミングと肺障害は、Tg+I/R, Quin+I/R グループで抑制された。結論：XO, PLA, は、小腸低灌流に続発する肺障害発生において、重要な役割を果たしていることが示唆された。

(日救急医会誌 1996; 7: 700-8)

キーワード：多臓器不全、成人型呼吸促進症候群、好中球、プライミング、小腸

¹ 日本医科大学付属千葉北総病院救命救急部
² Department of Surgery, Denver General Hospital, Colorado, USA

原稿受理日：1995 年 12月 12日 (95-092)