Amelioration of Postischemic Reperfusion Injury by Antiarrhythmic Drugs in Isolated Perfused Rat Lung

Kumuda C. Das and Hara P. Misra

Department of Biomedical Sciences, Virginia-Maryland Regional College of Veterinary Medicine, Virginia Polytechnic Institute, and State University, Blacksburg, Virginia

Antiarrhythmic drugs, such as lidocaine, quinidine, and procainamide, have been shown to be effective against postischemic reperfusion injury in isolated rat lungs. Rat lungs were perfused at a constant flow with Krebs-Henseleit buffer supplemented with 4% bovine serum albumin and ventilated with air containing 5% CO₂. The lungs were subjected to ischemia by stopping perfusion and ventilation for 60 min followed by 30 min of reperfusion. Lung injury was determined by measuring the increase in wet-to-dry lung weight ratio, while pulmonary arterial pressure and peak airway pressure were calculated from the pre- and postischemic differences. Lidocaine, quinidine, and procainamide at doses of 5, 10, and 20 mg/kg body weight, respectively, were found to attenuate the postischemic lung injury significantly (p<0.0001). The formation of cyclooxygenase products, which were elevated during reperfusion, was also significantly (p<0.0001) inhibited by these drugs. Since these antiarrhythmic agents are found to be powerful scavengers of hydroxyl radicals and can prevent membrane lipid peroxidation, these findings suggest that the antioxidant properties of these drugs may, in part, be responsible for protecting the lungs against reperfusion injury. — Environ Health Perspect 102(Suppl 10): 117–122 (1994)

Key words: lung, ischemia, reperfusion, lidocaine, quinidine, procainamide, local anesthetics, free radical, antiarrhythmic

Introduction

Lung transplant is rapidly becoming a clinical alternative for patients with end-stage lung disease. Preservation of the cadaver lung during transplant has been a major impediment to the wide clinical use of transplant procedures. Reperfusion of transplanted lungs previously subjected to brief period of ischemia causes irreversible tissue injury (1). Ischemia-reperfusion injury has been extensively studied in many organs, including brain, heart, intestine, and kidney (2–7). Little work has been done to elucidate the mechanism of reperfusion injury in the lung. Reactive oxygen species has been implicated in the etiology of ischemia-reperfusion injury (3,8–10). Antiarrhythmic drugs have been used as membrane stabilizers and were found to prevent microvascular permeability resulting from acute lung injury (11). The mechanism by which these antiarrhythmic agents diminish lung edema, however, is unclear and their ability to reduce postischemic reperfusion injury of the lung has not been tested. Recently we reported that antiarrhythmic agents such as lidocaine, quinidine, and procainamide are potent hydroxyl radical scavengers and were found to inhibit lipid peroxidation (12). Since free radicals of oxygen are important in initiating lipid peroxidation (13,14), and lipid peroxides are known to be produced during postischemic reperfusion of lung (15), we developed the hypothesis that antiarrhythmic drugs may protect lungs from reperfusion injury. Here we present evidence that antiarrhythmic drugs such as lidocaine, quinidine, and procainamide attenuate postischemic reperfusion injury in isolated perfused rat lung and these drugs were effective in preventing the accumulation of cyclooxygenase products during reperfusion of ischemic lung.

Materials and Methods

Ex Vivo Lung Preparation

Male Sprague-Dawley rats (Harlan's Sprague-Dawley, Dublin, VA) weighing 300 to 500 g were anesthetized with 64.8 mg/kg, ip, pentobarbital sodium (Anthony Products Co., Arcadia, CA). A tracheostomy was performed that permitted ventilation with a Harvard rodent ventilator (model 683) at 62 strokes per min, a tidal volume of 2.3 to 3 ml, and positive end expiratory pressure of 2.5 cm H₂O. The inspired gas mixture was air mixed with 5% CO₂ (Analyzed, Industrial Gas and Supply Co., Radford, VA). Subsequently a median sternotomy was performed, heparin (200 IU) was injected into the right ventricle, and cannulas were placed in the pulmonary artery and left ventricle. The heart, lungs, and mediastinal structures were removed en bloc and suspended from a Fort-250 rigid linear force transducer (World Precision Instruments, New Haven, CT) to monitor any weight change and placed in a humidified chamber. The lungs were perfused by a masterflex pump (Cole Parmer Instruments, Chicago, IL) with Krebs-Henseleit buffer at a constant flow of 0.05 ml/min/g bw. The Krebs-Henseleit buffer contained 118 mM NaCl, 4.7 mM KCl, 1.17 mM MgSO₄, 25 mM NaHCO₃, 1.18 mM KH₂PO₄, 1.90 mM CaCl₂, 11.1 mM glucose and 4% bovine serum albumin (66,000 mw, Sigma Chemical Co., St. Louis, MO). The pH of the perfusate was maintained between 7.35 and 7.45 by periodic addition of sodium bicarbonate.

The first 50 ml of lung effluents were discarded to eliminate circulating blood elements from the vascular space of the lung. Subsequently a recirculating mode was established with 50 ml of perfusate. Pulmonary artery pressure (Pa) was constantly monitored with a transducer blood pressure BPLR-0111 (WPI). Peak airway
pressure (Paw) was constantly monitored by a PNEU-01 (WPI) pressure transducer. The pressure transducers were calibrated with a blood pressure measurement instrument (The Lumiscope Co., [S-Nelkin Home Care, APCC] Edison, NJ).

Mean pulmonary Pa, change in lung weight, and mean peak Paw were constantly monitored through the pressure and linear force transducers connected to an amplifier bridge (WPI). The bridge was connected to a MacLab-4 (WPI) that in turn was connected to a Macintosh SE computer. The data were recorded by Scope version 3.1 software for the MacLab system (WPI).

**Induction of Lung Ischemia**

Isolated lungs were perfused for 10 min to ensure a stable preparation and were then subjected to ischemic injury for 60 min by stopping ventilation and perfusion. The lungs were inflated by instilling 2 ml of gas mixture into tracheal cannula before occlusion at the start of the ischemic period. Lung inflation was done to facilitate reperfusion after ischemia. Throughout the 60-min ischemia the lungs and perfusate were kept at 37°C.

**Lung Reperfusion**

Reperfusion after ischemic interval was started slowly and the flow rate was increased such that a mean pulmonary Pa of 14 mm Hg was never exceeded. Within 5 min of the onset of the reperfusion the perfusate flow was increased to the original flow rate present before the ischemic period (0.05 ml/min/g, bw). During reperfusion the perfusate reservoir and the lungs were maintained at 37 to 38°C. Lungs were reperfused for 30 min while they were ventilated with the same gas mixture.

**Experimental Groups**

Five experimental groups were studied. The first group of six lungs underwent 60 min of ischemia followed by 30 min of reperfusion. The same protocol was maintained for groups 2, 3, and 4 (n=6) with the exception that lidocaine, quinidine, and procainamide at 5, 10, and 20 mg/kg bw, respectively, were added to the perfusate. This dose was calculated taking the blood volume at 8% of the body weight. Group 5 served as control and underwent no ischemia. The drugs were added to the lung perfusate at the onset of lung perfusion prior to ischemia.

**Measurement of Lung Injury**

**Wet-to-Dry Lung Weight Ratio.** At the end of each experiment the left main stem bronchus was transected and the left lung was isolated for the determination of the wet-to-dry lung weight ratio. Lungs were weighed and placed in a convection oven (Model 605, Precision Scientific Inc., Chicago, IL) at 120°C and weighed daily for 3 days. Lung weight at 72 hr was reported as dry weight because no further weight loss occurred after that time.

**Pulmonary Artery Pressure.** Mean pulmonary Pa was monitored for 10 min during the preischemic period and entire postischemic period after the full flow was resumed. Percentage change was calculated taking the difference of the mean pre- and postischemic pulmonary artery pressures.

**Peak Airway Pressure.** Mean peak Paw was monitored for 10 min of preischemic period and 30 min during postischemic period. Percentage change was calculated taking the difference of pre- and postischemic pressures.

**Measurement of Cyclooxygenase Metabolites**

TXB2 and 6-keto-PGF1α, the stable metabolites of TXA2 and prostacyclin, respectively, were measured as indicators of cyclooxygenase metabolite production. Samples (1.8 ml) of pulmonary venous effluent were collected immediately before the onset of ischemia, and at 5, 10, and 20 min of reperfusion. Time-matched samples were also obtained in the uninjured controls. Measurements of TXB2 and 6-keto-PGF1α were made in thromboxane B2 [(H] and 6-keto-PGF1α[3H] scintillation proximity assay (SPA) systems [16]; Amersham International Plc, Amersham, UK) on methyl formate extracted samples in duplicate (Bakerbond C18; J. T. Baker, Inc., Phillipsburg, NJ).

**Statistical Analysis**

Values were expressed as mean ± SEM. Groups were compared using one-way analysis of variance and the Tukey's multiple comparison test using SAS statistical software (SAS Institute, Cary, NC). Data for PGF1α and TXB2 were analyzed by two-way analysis of variance taking preischemia and ischemia as factors. A p value of less than 0.05 was considered significant.

**Results**

**Effect of Antiarrhythmic Drugs on Wet-to-Dry Lung Weight Ratio**

Lung weight remained stable in uninjured control lungs during the 100 min of perfusion. Lungs subjected to ischemia reperfusion had increased lung weight at the end of 30 min of reperfusion as recorded by a MacLab-4 connected to a linear force transducer (data not shown). Wet-to-dry lung weight ratio, a measure of edema formation, was significantly higher (p<0.0001) in ischemia-reperfused lungs compared to uninjured controls (Figure 1). The antiarrhythmic drugs lidocaine, quinidine, and procainamide at single doses of 5, 10, and 20 mg/kg bw, respectively, significantly (p<0.0001) reduced the wet-to-dry weight ratios compared to ischemia-reperfused lungs (Figure 1).

**Effect on Pulmonary Pressure**

Pulmonary Pa remained stable over the 100 min of perfusion in the control lungs not subjected to ischemia. Lungs subjected to 60 min of ischemia were allowed to reach a stable Pa 10 min after the onset of reperfusion. The Pa was found to be significantly higher (p<0.0008) 10 min after the onset of reperfusion compared to the pressures present in the same lung during preischemia or compared to the Pa measured in the time-matched control lungs (Figure 2). The Pa remained elevated compared to preischemic values in the same lung at 10 and 30 min after the onset of reperfusion. Addition of lidocaine, quini-
Effects of antiarhythmic drugs on pulmonary arterial pressure of ischemic-reperfused rat lung. Uninjured control lungs were perfused for 100 min. Lungs subjected to ischemia-reperfusion underwent 10 min of preischemia followed by 60 min of ischemia and 30 min of reperfusion. Lidocaine, quinidine, and procainamide at doses of 5, 10 and 20 mg/kg bw, respectively, were added to the perfusion buffer at the beginning of perfusion. Results were expressed as percent change in mean pulmonary arterial pressure between preischemia and postischemic reperfusion. *p<0.001 and **p<0.008 compared to the control. For each treatment group, n=6.

Table 1. Effect of antiarhythmic drugs on cyclooxygenase product formation in isolated rat lung subjected to ischemia-reperfusion.

| Drug          | Preischemia | Postischemia | Preischemia | Postischemia |
|--------------|-------------|--------------|-------------|--------------|
| Control      | 220 ± 10    | 200 ± 20     | 58 ± 1.95   | 64 ± 1.47    |
| I/R          | 183 ± 15    | 1428 ± 315*  | 68 ± 1.28   | 132 ± 9.68*  |
| I/R + lidocaine | 205 ± 11    | 312 ± 63**   | 62 ± 1.68   | 85 ± 2.62**  |
| I/R + quinidine       | 250 ± 36    | 208 ± 73**   | 55 ± 1.75   | 63 ± 3.11**  |
| I/R + procainamide    | 251 ± 15    | 282 ± 74**   | 55 ± 2.90   | 65 ± 1.48**  |

*First 10 min of perfusion. Samples taken 5 min after reperfusion. Control lungs not subjected to ischemia but perfused for 100 min. 50-min ischemia followed by 30 min of reperfusion. Lidocaine, quinidine and procainamide at doses of 5, 10 and 20 mg/kg bw, respectively, were added to the perfusate at the beginning of perfusion. *p<0.001, compared to control; **p<0.001, compared to ischemia-reperfusion.

dine, and procainamide at 5, 10 and 20 mg/kg bw, respectively, significantly reduced the Pa respectively, of ischemia-reperfused lungs compared to untreated reperfused lungs (Figure 2).

Effect on Peak Airway Pressure

Peak Paw remained stable over the 100 min of perfusion in the uninjured control lungs. Lungs subjected to ischemia and reperfusion had a significantly higher (p<0.0001) Paw after 30 min of reperfusion. Lungs subjected to ischemia reperfusion but treated with lidocaine (5 mg/kg bw), quinidine (10 mg/kg bw), and procainamide (20 mg/kg bw) had significantly (p<0.0001) reduced Paw compared to the untreated ischemia-reperfused lungs. These data are presented in Figure 3.

Effect of Antiarrhythmic Drugs on Cyclooxygenase Product Formation

Measurements of 6-keto-PGF1α and TxB2 in lung effluents collected prior to ischemia and in the time-matched lung effluents from the uninjured control lungs showed no significant differences (Table 1). In the ischemia-induced lungs, 5 min of reperfusion resulted in 7- and 2-fold increases in the production of the cyclooxygenase metabolites, 6-keto-PGF1α and TxB2, respectively (Table 1). These increases were significantly (p<0.05) higher than either control preischemic lung or preischemic lungs with addition of drugs in the perfusate (Table 1). The time course of accumulation of these metabolites in lung effluents was studied at 5, 10, and 20 min postischemia. Both the 6-keto-PGF1α and TxB2 levels were found to remain elevated (p<0.0001) in the lung effluent collected up to 20 min after reperfusion compared to effluent collected from the same lung prior to ischemia and when compared to time-matched lung effluent samples from control lungs not subjected to ischemia (Figures 4, 5). Effluents collected at 5, 10, and 20 min after reperfusion from lungs subjected to ischemia reperfusion and treated with lidocaine, quinidine, and procainamide at 5, 10, and 20 mg/kg bw, respectively, had significantly less (p<0.0001) 6-keto-PGF1α and TxB2 compared to untreated lungs that were subjected to similar ischemia reperfusion conditions (Figures 4, 5). When the levels of PGF1α and TxB2 were compared in lungs subjected to ischemia and reperfusion, the levels of both cyclooxygenase metabolites were found to be significantly (p<0.05) higher 5 min after reperfusion, when compared to effluents collected at 10 or 20 min after reperfusion. The levels of PGF1α and TxB2 in effluents from lungs treated with the antiarrhythmic drugs were also compared, with no significant change observed in levels of PGF1α and TxB2 between quinidine and procainamide in effluents collected at 5, 10, or 20 min of reperfusion. However, the lungs treated with lidocaine had significantly higher (p<0.05) levels of PGF1α when compared with control lungs or lungs treated with quinidine or procainamide.

Discussion

A major source of damage in postischemic reperfusion injury is believed to be the generation of oxygen-free radicals and other toxic oxygen metabolites (9,17,18). These radicals and metabolites have been implicated in postischemic reperfusion injury in the heart, kidney, intestine, brain, and other organs (14,18–20). Studies in the postischemic reperfusion injury of the lungs also implicate toxic oxygen metabolite as a source of damage (8,17,21,22). In our present study, antiarrhythmic drugs,
such as lidocaine, quinidine, and procainamide, significantly reduced pulmonary edema, pulmonary Pa and Paw. These drugs also inhibited the formation of cyclooxygenase metabolites known to be produced during reperfusion of ischemic lungs (23). Although these agents have numerous systemic and local effects on various biological tissues, both in vivo and in vitro (24,25), their ability to ameliorate postischemic reperfusion injury in the lungs has not previously been recognized.

The mechanism by which the antiarrhythmic agents are effective against reperfusion injury may be explained, in part, by their antioxidant properties. In a recent study, Stelzner et al. (11) found that these drugs protect lungs against thiourea-induced injury in rats. As oxygen radicals are likely to be produced during metabolism of thiourea (11), these authors speculated an antioxidant action of antiarrhythmic drugs. However, they found that these drugs are not scavengers of O$_2^-$ or H$_2$O$_2$. Recently, we have demonstrated that these drugs are powerful hydroxyl radical scavengers ($k = 1.8 \times 10^{10}, 1.61 \times 10^{10}$ and $1.45 \times 10^{10}$ M$^{-1}$sec$^{-1}$ for quinidine, lidocaine and procainamide, respectively) and inhibitors of lipid peroxidation (12). Therefore, it is likely that these drugs protect pulmonary tissue against postischemic reperfusion injury by preventing lipid peroxide formation and/or scavenging OH$^{-}$.

The concentration of three antiarrhythmic drugs in the perfusate were 40, 120, and 250 µg/ml for lidocaine, quinidine, and procainamide, respectively. However, these drugs are also known to bind to plasma albumin, thereby reducing the availability of free drug for therapeutic action (26). Since our perfusate contained 4% bovine serum albumin, the actual concentrations of free drugs may be much less than indicated. The LD$_{50}$ and pharmacokinetics of these drugs have not yet been elucidated in rats. Taking into account the doses of 4, 20, and 30 mg/kg bw for lidocaine, quinidine, and procainamide in the study by Stelzner et al. (11), our doses of 40, 120, and 250 µg/ml for rats are significantly smaller. Detailed pharmacokinetic studies of these drugs in rats are needed to determine the typical nontoxic plasma levels of these drugs in rats.

Because toxic oxygen metabolites can directly cause cell injury or lead to the production of other mediators, such as arachidonate metabolites, we measured the effect of antiarrhythmic agents on the cyclooxygenase metabolites thromboxane and prostacyclin during the reperfusion of ischemic lungs. Postischemic reperfusion caused a significant elevation of both the thromboxane and prostacyclin levels as measured by their stable metabolites TxB$_2$ and 6-keto-PGF$_{10}$. Similar increases of these metabolites have been observed by Ljungman et al. (16). It is believed that cyclooxygenase

---

**Figure 4.** Effects of antiarrhythmic drugs on 6-keto-PGF$_{10}$ on ischemic-reperfused rat lung. Samples for 6-keto-PGF$_{10}$ measurements were obtained prior to ischemia as well as 5, 10, and 20 min after reperfusion or at time-matched points in control lungs not subjected to ischemia. Lidocaine, quinidine, and procainamide at 5, 10, and 20 mg/kg bw, respectively, were added to the perfusate at the beginning of the perfusion period. 6-keto-PGF$_{10}$ was measured by the scintillation proximity assay method on extracted samples in duplicate. $^*p<0.0001$ compared to control and drug-treated postischemic-reperfused lungs. $^{**}p<0.05$ when compared with control lungs or lungs treated with quinidine or procainamide but significantly lower than the ischemia-reperfused lungs. For each treatment group, $n=6$.

**Figure 5.** Effects of antiarrhythmic drugs on TxB$_2$ on ischemic-reperfused rat lung. Samples for TxB$_2$ measurements were obtained prior to ischemia as well as 5, 10, and 20 min after reperfusion or at time-matched points in control lungs not subjected to ischemia. Lidocaine, quinidine, and procainamide at 5, 10, and 20 mg/kg bw, respectively, were added to the perfusate at the beginning of the perfusion period. TxB$_2$ was measured by the scintillation proximity assay method on extracted samples in duplicate. $^*p<0.0001$ compared to control and drug-treated ischemia-reperfused lungs. For each treatment group, $n=6$. 
metabolites, produced secondary to the production of oxygen radicals, may in turn, cause tissue damage (16). However, these authors have concluded that cyclooxygenase metabolites may not be the sole source of injury because protection by inhibitors of cyclooxygenase product formation was not complete. Burghuber et al. (27) have also reported similar findings and concluded that cyclooxygenase products are not primarily responsible for lung damage. It has been shown that lidocaine is not an

inhibitor of prostaglandin biosynthesis in vitro (28), but rather increases the production of prostacyclin (29). Our data demonstrate that all these antiarrhythmic drugs inhibit cyclooxygenase product formation. Since \(-OH\) are known to be responsible for the release of arachidonic acid from membrane phospholipids (30), it is possible that these drugs may not inhibit prostaglandin formation per se but might inhibit the liberation of arachidonic acid from phospholipids by scavenging \(-OH\) radicals.

Nevertheless, the lung damage imposed by ischemia reperfusion could be the concomitant actions of both toxic oxygen products (21) and cyclooxygenase metabolites (23). We conclude that the inhibition of cyclooxygenase product formation and the attenuation of postischemic lung injury by these drugs may, in part, be due to the removal of toxic oxygen metabolites generated during the reperfusion of the lung.

**REFERENCES**

1. Haverich A, Scott WC, Jamieson SW. Twenty years of lung preservation: a review. J Heart Transplant 4:234-240 (1985).
2. Dempsey RJ, Roy MW, Meyer K, Cowen DE, Tai HH. Development of cyclooxygenase and lipooxygenase metabolites of arachidonic acid after transient cerebral ischemia. J Neurosurg 64:118-124 (1986).
3. McCord JM. Oxygen-derived free radicals in post-ischemic tissue injury. N Engl J Med 312:159-163 (1985).
4. Omamini T. Oxygen radicals, lipid peroxidation, and neutrophil infiltration after small-intestinal ischemia and reperfusion. Surgery 105:593-597 (1989).
5. Parks DA, Bulkley GB, Granger DN, Hamilton SR, McCord JM. Ischemic injury in the small intestine: role of superoxide radicals. Gastroenterology 82:9-15 (1982).
6. Slafer M, Kane PK, Krish MM. Superoxide dismutase plus catalase enhances the efficacy of hypothermic cardioplegia to protect the globally ischemic reperfused heart. J Thorac Cardiovasc Surg 83:830-839 (1982).
7. Simpson PJ, Todd III RF, Fantone JC, Michelson JK, Griffin JD, Lucchesi BR. Reduction of experimental canine myocardial reperfusion injury by monoclonal antibody (anti-mol, anti-CD116) that inhibits leukocyte adhesion. J Clin Invest 81:624-629 (1988).
8. Kennedy T, Rao N, Hopkins C, Tolkey E, Hoidal JR. Reperfusion injury occurs in the lung by free-radical mechanism. Chest 93:1495 (1988).
9. Martin D, Korthuis RJ, Perry M, Townsley MJ, Taylor AE. Oxygen radical mediated lung damage associated with \(\alpha\)-naphthylthiourea. Acta Physiol Scand, Suppl 548:119-125 (1986).
10. Weisfeldt ML. Reperfusion and reperfusion injury. Clin Res 2:311-319 (1987).
11. Stetner TJ, Welsh CH, Berger E, McCullough RG, Morris K, Repine JE, Weil JV. Antiarrhythmic agents diminish thioate-induced pulmonary vascular protein leak in rats. J Appl Physiol 63:1877-1883 (1987).
12. Das KC, Misra HP. Antiarrhythmic agents: scavengers of hydroxyl radicals and inhibitors of NADPH-dependent lipid peroxidation in bovine lung microsomes. J Biol Chem 267:19172-19178 (1992).
13. Bertrand Y. Oxygen-free radicals and lipid peroxidation in adult respiratory distress syndrome. Intensive Care Med 11:56-60 (1985).
14. Granger DN, Rutoli G, McCord JM. Role of superoxide radicals in intestinal ischemia. Gastroenterology 81:22-29 (1981).
15. Fisher AB, Dodia C, Tan Z, Iayene I, Eckenhoff RG. Oxygen-dependent lipid peroxidation during lung ischemia. J Clin Invest 88:674-679 (1991).
16. Udenfriend S, Gerber LD, Brink L, Spector S. Scintillation proximity radioimmunoassay utilizing 125I-labeled ligands. Proc Natl Acad Sci USA 82:8672-8676 (1985).
17. Granger DN, Hollwarth ME, Parks DA. Ischemia-reperfusion injury: role of oxygen derived free radicals. Acta Physiol Scand Suppl 548:47-63 (1986).
18. Marubayashi S, Dohi K, Ezaki H, Yamada K, Kawasaki T. Preservation of ischemic liver cells prevention of damage by coenzyme Q10. Transplant Proc 15:1297-1299 (1983).
19. Pallar MS, Hoidal JR, Ferris TF. Oxygen free radicals in ischemic acute renal failure in rats. J Clin Invest 74:1156-1164, 1984.
20. Zweier JR. Measurement of superoxide-derived free-radicals in the reperfused heart. Evidence for a free radical mechanism of reperfusion injury. J Biol Chem 263:1353-1357 (1988).
21. Jurmann M, Dammenhayn L, Schaeffers HJ, Haverich A. Pulmonary reperfusion injury: evidence for oxygen-derived free radical mediated damage and effects of different free radical scavengers. Eur J Cardiothorac Surg 4:665-670 (1990).
22. Kennedy TP, Rao NV, Hopkins C, Penington L, Tolley E, Hoidal JR. Role of reactive oxygen species in reperfusion injury of the rabbit lung. J Clin Invest 83:1326-1335 (1989).
23. Ljungman GA, Grum CM, Deeb GM,邦ling SF, Morganroth ML. Inhibition of cyclooxygenase metabolite production attenuates ischemia-reperfusion lung injury. Am Rev Respir Dis 143:610-617 (1991).
24. Arnsdorf MF. Electrophysiologic properties of antidysrhythmic drugs as a rational basis for therapy. Med Clin N Am 60:213-232 (1976).
25. Scherphof GL, Scarpa A, Van Toorenenberg A. The effects of local anesthetics on the hydrolysis of free and membrane bound phospholipids catalysed by various phospholipases. Biochim Biophys Acta 270:226-240 (1972).
26. Udassin R, Ariel I, Haskel Y, Kitrossky N, Chevion M. Salicylate as an in vivo free radical trap: studies on ischemic insult to the rat intestine. Free Radic Biol Med 10:1-6 (1991).
27. Burghuber O, Mathias ME, McMurtry IF, Reeves JT, Voelkel NF. Lung edema due to hydrogen peroxide is independent of cyclooxygenase products. J Appl Physiol 56:900-905 (1984).
28. Kunze HE, Bohn E, Vogt W. Effects of local anesthetics on prostaglandin biosynthesis in vitro. Biochim Biophys Acta 360:260-269 (1974).
29. Casey LC, Armstrong MC, Fletcher JR, Ramwell PW. Lidocaine increases prostacyclin in the rat. Prostaglandins 19:976-984 (1980).
30. Panganamala RV, Sharma HV, Heikkila RE, Geer JC, Cornell DG. Prostaglandins 11:599-60 (1976).