Reduction of the size of infarction by allopurinol in the ischemic-reperfused canine heart

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ABSTRACT This study was performed to assess the effect of allopurinol in a canine preparation of myocardial infarction. Dogs underwent occlusion of the left circumflex coronary artery for 90 min, followed by reperfusion for 6 hr. Three groups were studied: (1) control, (2) dogs receiving 25 mg/kg allopurinol 18 hr before occlusion and 50 mg/kg 5 min before occlusion, and (3) dogs receiving allopurinol as above plus 5 mg/kg superoxide dismutase over 1 hr beginning 15 min before reperfusion. Infarct size expressed as a percentage of the area at risk was 40 ± 4 in the control group, 22 ± 5 in the allopurinol group (p < .05 vs control), and 17 ± 4 in the allopurinol plus superoxide dismutase group (p < .05 vs control). The differences in infarct size were not due to differences in myocardial oxygen supply or demand. Neutrophil superoxide anion production was not altered by allopurinol treatment. The results suggest that myocardial xanthine oxidase may generate oxygen radicals that play a role in myocardial injury due to ischemia and reperfusion.


ACTIVATED SPECIES of oxygen, such as superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radical (•OH) may be responsible for the tissue damage from a diversity of causes, including radiation, inflammation, and ischemia.¹ In animal preparations, transient ischemia of the small intestine,² the kidney,³ and the heart⁴–⁶ results in injury that is diminished by agents that are known scavengers of oxygen radicals.

The possible sources of reactive oxygen metabolites after myocardial ischemia and reperfusion include activated neutrophils in the extracellular compartment,⁷ and the enzyme xanthine oxidase (xanthine: O₂ oxidoreductase EC 1.2.3.2).⁸ In previous experiments reported by this laboratory, depletion of neutrophils⁹ significantly reduced the extent of damage after a 90 min occlusion and 6 hr of reperfusion of the canine circumflex coronary artery. The results support the hypothesis that neutrophils are an important cause of damage within reperfused ischemic myocardium.⁷ ⁹ ¹⁰ The role of xanthine oxidase in the pathophysiology of myocardial infarction remains controversial.¹¹–¹³ Therefore, this study was performed to evaluate the effects of xanthine oxidase inhibition by allopurinol in a canine preparation of myocardial infarction.

Methods

Evaluation of ischemic injury. Detailed methods have been published previously.⁹ Male mongrel dogs (12 to 17 kg) were anesthetized with Dial-urethane (0.6 ml/kg iv) and ventilated with room air. After thoracotomy, the proximal left circumflex coronary artery (LCX) was affixed with an electromagnetic flow probe. A critical stenosis of silt suture was placed to reduce the incidence of reperfusion arrhythmias.¹⁴ Left atrial pressure, carotid arterial pressure, LCX blood flow, and the lead II electrocardiogram were recorded continuously.

Three groups were studied: (1) the control group (n = 14), (2) dogs that received 25 mg/kg allopurinol (Sigma) 18 hr before occlusion and 50 mg/kg 5 min before occlusion (n = 12), and (3) dogs that received allopurinol as above plus 5 mg/kg superoxide dismutase (SOD) (3000 U/mg, Sigma) (n = 8). Allopurinol (dissolved in 50 ml of 0.9% sodium chloride, pH 10.3 to 10.6) and the control solution (50 ml of 0.9% sodium chloride, pH 10.3 to 10.6) were injected by peripheral vein at a rate of 10 ml/min. SOD (dissolved in 60 ml of 0.9% sodium chloride) was infused via the left atrial appendage at 1.0 ml/min for 60 min beginning 15 min before reperfusion of the LCX.

The experimental protocol consisted of a 90 min occlusion and 6 hr reperfusion of the LCX. Predetermined exclusion crite-
ria were: heart worms, no manifestations of ischemia (no ST segment elevation after LCX occlusion or arrhythmias upon reperfusion), and intractable ventricular fibrillation. After the 6 hr reperfusion period, the heart was fibrillated electrically and excised. With the use of a dual perfusion technique previously described, \(^4\) the aorta was perfused in a retrograde manner with 0.25% Evans Blue dye, and the LCX was perfused with 1.5% triphenyltetrazolium chloride (TTC) in 20 mM potassium phosphate buffer (pH 7.4, 37°C). The solutions were infused simultaneously for 5 min at 100 mm Hg with the heart suspended in a water bath (37°C). The heart was cut into 1 cm thick transverse sections and fixed in 10% formalin. An investigator who was unaware of the treatment group (M. J. S.) traced and dissected the sections to allow quantitation of the infarct zone, area at risk, and left ventricle by both gravimetric and planimetric methods.

Samples from the TTC-negative tissue along with the adjacent TTC-positive border were embedded in paraffin, cut into 5 μm thick sections, and stained with hematoxylin and eosin. A pathologist (G. D. A.) who was unaware of the treatment protocol graded the samples on a semiquantitative 0 to 4+ scale for microscopic evidence of necrosis, leukocyte infiltrate, and hemorrhage.

**Evaluation of regional myocardial blood flow (RMBF).** A separate group of six dogs treated with the allopurinol schedule described above was used to study the drug’s effect on RMBF. As described previously, radioactive microspheres (15 μm in diameter, New England Nuclear, Boston) labeled with \(^{141}\)Ce, \(^{103}\)Ru, or \(^{46}\)Sc were used to assess RMBF. \(^5\) Before their administration, the microspheres were placed in an ultrasonic bath and agitated with a vortex mixer. An aliquot of 1 to 2 million microspheres was diluted in 1 ml of saline (37°C) and infused via the left atrial appendage over 30 sec. Each injection was flushed twice with 10 ml of saline. Dual reference blood samples were withdrawn simultaneously from one femoral and one carotid artery at 4.26 ml/min. RMBF was assessed at three times: before occlusion (before the second dose of allopurinol), 10 min after occlusion, and 80 min after occlusion. After staining ex vivo as described above and fixation in 10% formalin, the infarct zone and area of risk of each slice of the left ventricle were traced for planimetric analysis. The transverse sections were then cut into epicardial, midmyocardial, and endocardial sections of the infarct zone and noninfarcted left ventricle. Radioactivity of the tissue and blood samples were determined with a TRACOR model 1185 gamma spectrometer. Overlap corrections and calculations of RMBF were made with an Apple II+ computer.

**Evaluation of neutrophil superoxide production.** Three additional animals were used to assess the effect of allopurinol on neutrophil \(O_2^-\) production. Neutrophils were purified from heparinized whole canine blood with a Ficoll-hypaque discontinuous density gradient. \(^6\) After lysis of erythrocytes with ammonium chloride and washing with Hank’s balanced salt solution, microscopic examination of the purified neutrophil suspension revealed less than 2% contamination with other cells. The concentration was then adjusted to 2.5 × 10⁶ cells/ml. After stimulation of the cells with phorbol myristate acetate (100 ng/ml, 37°C), the maximal rate of \(O_2^-\) formation was calculated from the SOD-inhibitable reduction of ferricytochrome C recorded at 550 nM with an extinction coefficient of 21.1 cm⁻¹ mM⁻¹.

**Statistics.** All data are expressed as mean ± SEM. Differences were considered significant at \(p < .05\). Variables measured once (percentage of area at risk infarcted, percentage of left ventricle infarcted, and area at risk/left ventricle) were compared by analysis of variance and Newman-Keuls multiple-range test. The hemodynamic variables were initially analyzed with a profile analysis that included the following time points: before allopurinol (second dose), before occlusion, 15, 30, 60, and 90 min after occlusion, and 2, 4, and 6 hr after reperfusion. \(^6\) For analyses indicating time-treatment interactions analyses of variance and Scheffe’s multiple comparison method confidence intervals were computed for each time point. Pairwise comparisons of RMBF were made by Student’s t test for paired data and a Bonferroni experiment-wise \(\alpha\)-error protection rate. Fisher’s exact test was used to compare the incidence of ventricular fibrillation.

**Results**

**Reduction of ischemic myocardial injury.** A total of 35 animals was studied. Nine animals did not satisfy the criteria for myocardial ischemia (six control and three drug-treated dogs). Two animals failed to complete the protocol due to intractable ventricular fibrillation (one control and one allopurinol-treated dog). One animal was excluded because of the detection of heart worms after its death. Therefore, the final groups consisted of eight controls, eight treated with allopurinol alone, and seven treated with allopurinol and SOD.

The incidence of ventricular fibrillation during coronary occlusion was significantly higher in the control group than in the treatment groups (4 vs 0; \(p < .01\)). Only two animals developed ventricular fibrillation after reperfusion (one in each drug group). The infrequent occurrence of reperfusion ventricular fibrillation was a consequence of the LCX stenosis, which reduces hyperemia during reperfusion. \(^4\)

As demonstrated in previous studies by this laboratory, \(^6\) results of the gravimetric and planimetric methods of quantifying infarct size were in close agreement. For infarct zone/area at risk, the equation for linear regression was planimetric = 0.97 (Gravimetric) + 2.24 (r = .97, SE = 4.45, n = 23). By both the planimetric and gravimetric (figure 1) methods of analysis, infarct size was significantly smaller for both drug groups (\(p < .05\) vs control), whether infarct size was expressed as a percentage of the total left ventricle or area at risk. Although infarct zone/left ventricle was 40% smaller after allopurinol alone and 65% smaller after allopurinol plus SOD, the difference between the allopurinol and allopurinol/SOD groups was not statistically significant.

As reported previously, \(^1\) transient tachycardia was observed after the 50 mg/kg dose of allopurinol, but there were no significant differences between groups during occlusion or reperfusion with respect to heart rate or mean arterial pressure (table 1).

**RMBF.** Infarct size as a percentage of the area at risk was similar for the allopurinol group receiving microspheres (20%) and the allopurinol group that did not (25%). Measurement of RMBF after 10 and 80 min of
LCX occlusion showed severe ischemia of the LCX bed at both time points (table 2).

**Histologic analysis of risk region.** The histologic examination of TTC-negative tissue revealed contraction band necrosis, alteration of nuclei, and infiltration with inflammatory cells, which agrees with previous work validating the TTC technique of quantifying infarct size. The degree of leukocyte infiltrate as determined on a semiquantitative scale was variable, with no difference between groups.

**Neutrophil superoxide production.** Neutrophil $O_2^{-}$ production measured as nanomoles per minute per $2.5 \times 10^6$ cells was $22.6 \pm 2.6$ before and $23.2 \pm 4.8$ after treatment of the donor animals with allopurinol ($p > .05$).

**TABLE 1**  
Hemodynamic data

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Preocclusion</td>
<td>131 ± 7</td>
<td>119 ± 6</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>End occlusion</td>
<td>143 ± 7</td>
<td>112 ± 6</td>
</tr>
<tr>
<td></td>
<td>End reperfusion</td>
<td>176 ± 9</td>
<td>105 ± 5</td>
</tr>
<tr>
<td>ALLO</td>
<td>Preocclusion</td>
<td>142 ± 9</td>
<td>113 ± 7</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>End occlusion</td>
<td>152 ± 10</td>
<td>112 ± 11</td>
</tr>
<tr>
<td></td>
<td>End reperfusion</td>
<td>181 ± 14</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>ALLO/SOD</td>
<td>Preocclusion</td>
<td>141 ± 8</td>
<td>137 ± 6</td>
</tr>
<tr>
<td>(n = 7)</td>
<td>End occlusion</td>
<td>160 ± 9</td>
<td>116 ± 8</td>
</tr>
<tr>
<td></td>
<td>End reperfusion</td>
<td>192 ± 5</td>
<td>109 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. ALLO = allopurinol.

**TABLE 2**  
RMBF in the ischemic bed (ml/min/g; n = 6)

<table>
<thead>
<tr>
<th></th>
<th>Endocardial</th>
<th>Midmyocardial</th>
<th>Epicardial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preocclusion</td>
<td>1.046 ± 0.115</td>
<td>0.904 ± 0.110</td>
<td>0.817 ± 0.075</td>
</tr>
<tr>
<td>Early occlusion</td>
<td>0.042 ± 0.007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.067 ± 0.011&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.109 ± 0.016&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Late occlusion</td>
<td>0.031 ± 0.008&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.067 ± 0.014&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.155 ± 0.027&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.  
<sup>a</sup>p < .05 vs preocclusion.

**Discussion**

This study demonstrates that pretreatment (18 hr before myocardial ischemia) with allopurinol, an inhibitor of xanthine oxidase, reduces by 40% the extent of myocardial injury after regional ischemia for 90 min and reperfusion for 6 hr. Previous studies of allopurinol and infarct size have had conflicting results, but several explanations emerge when they are compared.

During reperfusion, the reintroduction of molecular oxygen to hypoxic myocardium may facilitate the production of oxygen radicals by xanthine oxidase. Therefore, by measuring infarct size after a permanent coronary occlusion, Shatney et al. may have inadvertently obviated free radical production by xanthine oxidase, precluding both xanthine oxidase-mediated myocardial injury and the beneficial effects of xanthine oxidase inhibition by allopurinol.

The disparate outcomes of investigations regarding allopurinol may also relate to the use of different schedules of drug administration. In two negative studies, no reduction of infarct size was found when treatment with allopurinol was started 15 min after a permanent coronary occlusion or 30 min before a 40 min occlusion of the LCX followed by 4 days of reperfusion. In contrast, infarct size was significantly smaller after 60 min of regional ischemia when treatment with allopurinol was begun 24 hr earlier. Similarly, pretreatment with allopurinol 1 day before coronary artery occlusion decreased the incidence of ischemic ventricular fibrillation in this study and that of reperfusion ventricular fibrillation in two others, while no antiarrhythmic effect was observed without pretreatment.

Therefore, the efficacy of allopurinol may depend on initiation of therapy earlier than the regimens employed by Reimer and Jennings or Shatney et al. The reason for such a requirement may be that efficacy requires sufficient time for accumulation of alloxanthine, the metabolite of allopurinol. Experimental dosing regimens (long-term) that allow for accumulation of alloxanthine are more likely to result in an inhibition of xanthine oxidase. The plasma half-life of allopurinol is 40 min, as compared with the half-life of its
active metabolite alloxanthine (18 to 30 hr). Furthermore, the parent compound, allopurinol, despite its avid binding to the enzyme xanthine oxidase, is a competitive inhibitor of the enzyme and theoretically, its inhibitory action could be overcome by hypoxanthine and xanthine, the accumulated products of ATP catabolism. In contrast, the active metabolite alloxanthine is a noncompetitive inhibitor and would prevent enzymatic activity despite the presence of enzyme substrate. On the basis of these pharmacokinetic considerations, it may be possible to explain the apparent discrepancy that exists in the literature regarding the efficacy of allopurinol in the prevention of myocardial reperfusion injury.

There are, however, additional methodologic issues that merit consideration. One is whether the beneficial effect of allopurinol observed in this study represents delay rather than prevention of necrosis. This concern arises from the observation that flurbiprofen, an anti-inflammatory agent, reduced infarct size that was determined after 6 but not that determined after 24 hr of permanent coronary artery occlusion. Although in this study we did not examine infarct size 24 hr after occlusion, the duration of ischemia was only 90 min and was followed by a 6 hr period of reperfusion. Reperfusion may initiate free radical–mediated damage that is superimposed on ischemic injury, but it arrests the advancing wavefront of ischemic cell death. Consequently, untreated animals subjected to a 90 min coronary occlusion have the same extent of infarction whether reperfusion is maintained for 6 hr or 24 hr. Also, treatment with scavengers of oxygen radicals reduces infarct size by a similar degree in dogs killed 6 hr and those killed 24 hr after a 90 min period of ischemia.

Another methodologic question is whether absence of TTC staining is an adequate index of tissue necrosis. Vivaldi et al. performed electron microscopy of TTC-stained and unstained areas of myocardium subjected to 6 hr of ischemia. Ultrastructural evidence of irreversible injury was found only in TTC-negative areas. Several studies documented an excellent correlation between quantitative evaluation of infarct size by TTC staining and histopathology. This laboratory has demonstrated a close correlation between infarct size quantitation with nitroblue tetrazolium (NBT), another dehydrogenase histochemical reagent, and depletion of myocardial creatine kinase activity. Measurement of infarct size by NBT and an infarct-avid radionuclide also yielded congruent results. Nevertheless, it is possible that TTC may overestimate tissue salvage by pharmacologic agents because ad-

mixture of reversibly and irreversibly damaged tissue at the border of the TTC-positive zone may cause slight underestimation of the area of small infarcts.

Finally, collateral blood flow was determined for only one subset of the animals reported in this study. The mean values of heart rate and blood pressure (table 1) indicate that the randomization process resulted in groups with comparable baseline myocardial oxygen demand. Randomization should also result in groups with ischemia of equivalent severity, but baseline measurement of collateral blood flow in each animal would be necessary to confirm that the differences in infarct size were not due to ischemia of different severity. In previous studies by this laboratory, collateral blood flows were similar to the measurements obtained in this study, and infarct size in the control group was equivalent to that in the control group in this study. The comparable results suggest that in the present study: (1) the severity of ischemia was not unusually severe in the control group, and (2) the severity of ischemia was not exceptionally mild in the subset of allopurinol-treated animals in which collateral blood flow was evaluated. Therefore, it seems unlikely that differences in baseline collateral blood flow would account for the different infarct sizes in the control group (infarct zone/area at risk = 42%) and the subset of the allopurinol group with known collateral flows (infarct zone/area at risk = 25%).

The impetus for the initial investigations of allopurinol’s effect on myocardial injury was the hypothesis that inhibition of xanthine oxidase might enhance ATP repletion by preventing catabolism of purine precursors. Reperfusion of the ischemic myocardium would probably wash out most of the accumulated purines, however, and thereby offset any potential effect of xanthine oxidase inhibition on the tissue’s capacity to synthesize ATP. In addition, the relationship between cell death and loss of ATP is controversial.

Renewed interest in the use of allopurinol as a myocardial protective agent evolved from the hypothesis that conversion of xanthine dehydrogenase to xanthine oxidase might result in oxygen radical production within reperfused ischemic tissues. Studies in vitro clearly show that xanthine oxidase–derived oxygen metabolites damage myocardial structure and function. The lack of techniques suitable for measuring free radical production in vivo, however, precludes direct proof that allopurinol protects reperfused ischemic tissue by preventing generation of oxygen radicals. In the present study, the reduction of myocardial injury by allopurinol was not significantly enhanced by addition of SOD, which is indirect evidence that the
effect of allopurinol is related to oxygen radical–mediated events. Also, treatment with allopurinol before the onset of myocardial ischemia and reperfusion limits depletion of catalase and glutathione, an indication of diminished generation of oxygen radicals.35

The site and nature of myocardial damage ensuing from xanthine oxidase activity remains undetermined. In experimental studies of ischemic intestine36 and skeletal muscle37 it was found that the increased vascular permeability observed after reperfusion was attenuated by pretreatment with free radical scavengers or allopurinol. The results suggest that oxygen radicals formed by xanthine oxidase may be the primary cause of the vascular injury after ischemia and reperfusion. Within myocardium, purine nucleoside phosphorylase activity and xanthine oxidase activity take place in vascular endothelial cells rather than myocytes.38 Consequently, both production of hypoxanthine and formation of oxygen radicals via oxidation of hypoxanthine may be confined to the vascular endothelium. Therefore, vascular damage by xanthine oxidase–derived oxygen radicals may be one cause of the “no reflow” phenomenon observed after reperfusion of ischemic myocardium.39

Inhibition of xanthine oxidase may also be of benefit because it prevents other potentially deleterious effects of xanthine oxidase activity. For example, xanthine oxidase liberates free iron by reduction of ferritin.40 By inhibiting ferritin reduction, a xanthine oxidase inhibitor may curtail iron-catalyzed formation of hydroxyl radicals and the ensuing peroxidation of lipids that may damage cell membranes.1, 41 Peroxidation of plasma membrane lipids by xanthine oxidase–derived oxygen radicals may also contribute to the release of chemotactic factors for neutrophils by damaged myocardium.42, 43 Therefore, more direct methods of quantitating neutrophils than the one used in this study might demonstrate that inhibition of xanthine oxidase attenuates neutrophil infiltration of ischemic myocardium, a recently elucidated approach to limitation of myocardial injury due to ischemia and reperfusion.7, 9, 40

The results obtained in this study are compatible with the effects of allopurinol in other preparations of ischemia and reperfusion. Recovery of canine left ventricular function after global ischemia and reperfusion was improved by pretreatment with allopurinol.44 In the rabbit isolated heart, allopurinol reduced the release of creatine kinase after hypoxia and reoxygenation.45 Pretreatment with allopurinol also decreased the renal dysfunction produced by temporary occlusion of the renal artery in rats2 and the mucosal necrosis of cat intestine rendered transiently ischemic.2

Although xanthine oxidase–derived oxygen radicals appear to play an important role in the development of reperfusion injury, activated neutrophils may also be an important cause of damage during reperfusion. Neutrophils accumulate within reperfused ischemic myocardium,10, 46 and may contribute to the “no reflow” phenomenon due to entrapment within capillaries.47 Depletion of neutrophils limits the extent of infarction after myocardial ischemia and reperfusion,9, 48 possibly by attenuating both capillary plugging and oxygen radical–mediated injury to myocytes and endothelial cells.

Preliminary reports indicated that allopurinol may inhibit macrophage chemotaxis and release of oxygen radicals,49, 50 but the data presented in this article agree with recent experiments that did not detect an inhibitory effect of allopurinol on neutrophil function.51 Therefore, allopurinol alone may confer incomplete protection against oxygen radicals during reperfusion of ischemic myocardium. A combination of agents that inhibits both xanthine oxidase and neutrophils might provide additive protection. For example, treatment of dogs during early reperfusion with N-2-mercaptopyropionyl glycine (MPG), a presumptive free radical scavenger, enhanced the degree of myocardial salvage by neutrophil depletion.52

In addition to reducing infarct size after prolonged ischemia (90 min), both MPG and the combination of SOD and catalase have been shown to improve the return of myocardial function after a brief (15 min) period of regional ischemia.53, 54 Therefore, oxygen free radicals also may contribute to the pathogenesis of postischemic ventricular dysfunction, or “stunned myocardium.”

The clinical implications of this and other investigations are that oxygen radicals produced by xanthine oxidase and other sources may exacerbate myocardial injury after resolution of a transient ischemic event. Therefore, the recovery of ventricular function after global ischemia during cardiopulmonary bypass and regional ischemia during coronary spasm or thrombosis may be improved by scavengers of free radicals. Therapy with free radical scavengers may prove a useful addition to current techniques of cardioplegia, coronary thrombolysis, and coronary angioplasty.

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