Effects of Isoproterenol on Distribution of Perfusion in Embolized Dog Lungs

J. W. Shepard, Jr., D. Hauer, V. Sgroi, and K. M. Moser

University of California at San Diego, San Diego, California

In 19 mechanically ventilated, anesthetized dogs, autologous venous thrombi were formed in the inferior vena cava and subsequently released. Serial perfusion lung scintigrams revealed the postembolic distribution of pulmonary blood flow before, during, and after the infusion of isoproterenol at 2.2 µg/min. Isoproterenol failed to restore perfusion to embolically occluded regions. When reperfusion occurred it was attributable to clot resolution.

Gas exchange and hemodynamic measurements obtained in seven thromboembolized animals showed no scan evidence of reperfusion during the isoproterenol infusion. After embolization, cardiac output increased from 1.7 to 2.6 liter/min (p < 0.05), and P\textsubscript{a}O\textsubscript{2} from 38.0 to 45.3 mm Hg (p < 0.05). Shunt fraction remained unchanged. The postembolic infusion of isoproterenol was associated with a further increase in cardiac output to 3.6 liter/min (p < 0.01), an elevation in P\textsubscript{a}O\textsubscript{2} to 50.7 mm Hg, along with a decrease in pulmonary vascular resistance from the postembolic mean of 448 to 246 dynes·sec·cm\textsuperscript{-5} (p < 0.05).

Perfusion defects following acute pulmonary thromboembolization are not altered by the infusion of the potent pulmonary vasodilator, isoproterenol. Infusion of this drug following thromboembolization may have potential therapeutic benefit by reducing pulmonary vascular resistance, increasing cardiac output, and elevating the mixed-venous oxygen tension.


Over the past 15 years, lung perfusion scintigraphy has become widely recognized as a useful test in establishing a diagnosis of thromboembolic obstruction of the pulmonary vascular bed (1,2). Although this procedure is relatively sensitive in detecting areas of regional hypoperfusion, it lacks specificity in determining the cause of an area of depressed perfusion (3,4). Regional hypoperfusion is commonly seen in disease processes associated with either radiographic infiltrates (5,6) or regional alveolar hypoxia (7) as well as in pulmonary thromboembolism. However, there is evidence suggesting that regional hypoperfusion secondary to hypoxic vasoconstriction in man (8,9) and dogs (10) is reversible with the administration of isoproterenol. Moreover, Goldzimer et al. (6) have reported that isoproterenol reversed the initial perfusion defect seen with experimentally induced canine pneumococcal pneumonia. Although pulmonary thromboemboli are currently considered to reduce perfusion by mechanical vascular obstruction, active vasoconstriction secondary to the release of serotonin, histamine, or other vasoactive agents could also contribute. If mechanical obstruction

Received Feb. 19, 1979; revision accepted April 12, 1979.
For reprints contact: J. W. Shepard, Jr., GRECC (111G JB), Veterans Administration Hospital, St. Louis, MO 63125.
due to emboli were the dominant mechanism involved in regional hypoperfusion, infusion of isoproterenol should not reverse the perfusion defects. In contrast, such infusion should reverse defects due to processes that promote regional pulmonary vascular constriction. Such a differential effect has potential diagnostic usefulness. Furthermore, isoproterenol might improve hemodynamics and systemic oxygenation by reducing pulmonary vascular resistance, increasing cardiac output and thereby improving systemic oxygen delivery. To test these hypotheses we have studied the effects of infusing isoproterenol in dogs following acute pulmonary thromboembolization.

MATERIALS AND METHODS

Animal selection. Nineteen mongrel dogs (18–34 kg) were selected for subsequent autologous thromboembolization if they met the following criteria: (a) normal chest radiograph, (b) normal supine perfusion lung scintigram, and (c) an arterial oxygen tension of greater than 500 mm Hg while breathing 100% oxygen. These data were acquired during anesthesia with intravenous sodium thiamylal (12.5 mg/kg body weight) 24–72 hr before thromboembolization.

Experimental preparation. All animals were anesthetized intravenously with sodium pentobarbital (28 mg/kg body weight), intubated, placed in the supine position, and mechanically ventilated with a Harvard animal ventilator at a tidal volume of 15 ml/kg body weight, with respiratory rate adjusted to maintain an arterial carbon dioxide tension of 35 ± 5 mm Hg. The lungs were hyperinflated to 45 ml/kg every 15 min. Polyethylene catheters were placed in two peripheral limb veins for infusions of anesthetic, isoproterenol, and radionuclide. The aorta was cannulated with a polyethylene catheter and a No. 7 Swan–Ganz catheter was placed in the pulmonary trunk. Anesthesia was maintained with intravenous sodium pentobarbital, 50–100 mg, as required to abolish the corneal reflex.

Preparation of clot. A 5- to 7-cm segment of the inferior vena cava (I.V.C.), extending from below the renal veins to the iliac bifurcation, was transabdominally isolated. A clot was then formed according to a modification of Wessler's technique (11). One minute after completion of a rapid intravenous injection of 60 ml of defibrinated human plasma, the exposed segment of the I.V.C. was ligated proximally and distally to allow the clot to form. If manual palpation confirmed the presence of clot, 30 min were allowed for clot maturation, during which time all pre-thromboembolization data were collected. After removal of the I.V.C. ligatures, the vein was massaged to ensure that none of the performed clot remained in the venous segment.

Protocol for isoproterenol infusion. One milligram of isoproterenol hydrochloride was added to 500 ml of normal saline and infused intravenously with a Harvard variable-infusion pump at a rate of 1.1 ml/min, delivering an infusion dosage of 2.2 μg/min. The isoproterenol infusion was begun approximately 30 min after thromboembolization and continued for 30 min, then discontinued.

Protocol for lung perfusion scint photographs. Perfusion scintigrams of the lung were obtained using a scintillation camera with a high-energy parallel-hole collimator. Images were displayed in analog form on an oscilloscope and recorded on Polaroid film and on magnetic tape interfaced to a digital computer for off-line analysis.

All perfusion scintigrams were performed with the animals in the supine position on a Plexiglas table placed directly over the scintillation camera. Radionuclide administration was via a peripheral limb vein. The screening lung perfusion scintigram was obtained 1 to 3 days before thromboembolization by the injection of 1 mCi of Tc-99m-labeled human albumin microspheres (HAM) and acquiring 100,000 counts. If this screening scintigram was considered normal by visual inspection, and the other selection criteria were fulfilled, the animal was entered into the thromboembolization–isoproterenol infusion protocol.

The 19 animals with normal screening images underwent thromboembolization followed by the intravenous infusion of isoproterenol. Serial perfusion scintigrams were obtained according to the following protocol. Thirty minutes after thromboembolization, 300 μCi of Tc-99m HAM (low-dose Tc scan) was injected intravenously and 100,000 counts acquired. The isoproterenol infusion was then begun. After 15 min of constant infusion, a 60-sec background image was obtained using the Tc window. One mCi of Tc-99m HAM was then given intravenously and counts obtained over 1 min (high-dose Tc scan). The computer was then made to subtract background from the high-dose Tc scan to obtain a scintigram representing the distribution of perfusion during the isoproterenol infusion.

In nine animals, a third perfusion scintigram was obtained 15 min after discontinuing the isoproterenol infusion. For this, 300 μCi of I-131 macroaggregated albumin were given i.v., adjusting the camera to an I-131 window and acquiring 100,000 counts.

All serial lung perfusion scans were obtained while the animal's position remained constant with respect to the scintillation camera. Visual analysis was performed independently by two experienced observers. In those few cases in which concordance
between observers was not obtained, a third observer cast the deciding vote.

Post-thromboembolization perfusion defects were categorized according to location: left, right, upper, middle, or lower lung fields. Each subsequent perfusion scan was compared with the antecedent perfusion scan, and perfusion defects were judged to have undergone (a) no reperfusion, (b) partial reperfusion, or (c) total reperfusion. Thus the perfusion scans obtained during isoproterenol infusion were compared with the initial postthromboembolization scans, and the post-isoproterenol scans were compared with those obtained during the isoproterenol infusion.

**Hemodynamic measurements.** In seven animals showing no evidence of scan reperfusion during the isoproterenol infusion, sequential measurements of pulmonary arterial systolic, diastolic, mean, and wedge pressures were obtained, and also of cardiac output. The pulmonary arterial pressures were monitored with an indwelling No. 7 Swan-Ganz catheter and a Statham 23 db pressure transducer placed at mid-chest level and connected to an amplifier and photographic recorder. Cardiac outputs were measured in duplicate by green-dye technique. Control measurements were made following clot formation in the I.V.C. and before thromboembolization. Subsequent measurements were made after embolization and during the isoproterenol infusion.

**Gas-exchange measurements.** In the same group of seven hemodynamically monitored animals showing no scintigraphic evidence of reperfusion, arterial and mixed-venous blood were sampled (a) in the control period (after I.V.C. clot formation but before thromboembolization); (b) after embolization but before isoproterenol; and (c) during the infusion of isoproterenol. At each interval, measurements were made during ventilation with room air and after 15 min on 100% oxygen. Samples were obtained anaerobically in preheparinized syringes for the measurement of arterial and mixed-venous oxygen and carbon dioxide tensions and pH, with the bath temperature of the blood-gas analyzer set at 39°C and temperature corrections for the gas tensions and pH made according to Kelman and Nunn (12). The arterial and mixed-venous oxygen contents were also measured. Because all arterial oxygen tensions were greater than 250 mm Hg with the animal breathing 100% O₂, shunt fractions were computed according to the following equation (13).

\[
\frac{Q_s}{Q_t} = \frac{0.003(P_aO_2 - P_aO_2)}{0.003(P_aO_2 - P_aO_2) + (CaO_2 - CvO_2)}
\]

Pulmonary vascular resistance was calculated as the difference between the mean pulmonary arterial and wedge pressures divided by the cardiac output.

**Statistical analyses.** The sequential observations made were subjected to analysis of variance, and if the F value was significant (p < 0.05), a double-tailed t-test for paired data was performed.

**RESULTS**

**Lung perfusion scintigrams.** Table 1 presents the anatomical distribution of the observed post-emboembolization perfusion defects and the extent of reperfusion of these defects during the isoproterenol infusion. Thirty-seven perfusion defects were observed in the 19 thromboembolized dogs. Five of the animals showed bilateral perfusion defects. No perfusion defect was observed in Animal 9, who at autopsy had a massive embolus extending from the right ventricle into the pulmonary trunk.

**Response to isoproterenol.** Dog 11 died as isoproterenol infusion was initiated. Of the remaining 34 perfusion defects, 23 (67%) showed no change after 30 min of isoproterenol infusion. However, there was partial reperfusion of seven defects (21%) and total reperfusion of four (11%).

**Post-isoproterenol data.** In the nine animals (Dogs 6, 7, 12, 14–19) in whom a third image was obtained after cessation of isoproterenol, there was no change from the perfusion pattern observed during infusion. These animals produced six of the seven defects showing partial reperfusion during isoproterenol, and two of the four defects with total return of perfusion. In all of the nine instances, the post-isoproterenol scan was identical to that obtained during isoproterenol.

**Hemodynamics.** In the seven animals showing no evidence of scan reperfusion with isoproterenol, we observed a significant increase in pulmonary artery mean pressure and cardiac output following embolization (Table 2). The small increases in pulmonary vascular resistance and wedge pressure were not significant. However, the postembolic infusion of isoproterenol was associated with an additional increase in cardiac output as well as a significant fall in pulmonary vascular resistance (Table 2). Pulmonary arterial mean pressure remained elevated, unchanged from the postembolic level, and a further small rise in the pulmonary arterial wedge pressure was noted.

**Gas exchange.** Following thromboembolization, PaO₂ fell 11.1 mm Hg and shunt fraction rose slightly. Although neither of these changes was statistically significant, the mixed-venous oxygen tension increased significantly by 7.3 mm Hg (Table 3).
After embolization, the isoproterenol infusion produced no significant changes in shunt fraction or PaO₂ from either the control or postembolic levels (Table 3). The mixed-venous oxygen tension rose by an additional 5.4 mm Hg, remaining significantly elevated over the control value.

After embolization, arterial pH decreased to 7.29 ± 0.03 from its control value of 7.36 ± 0.03 (p < 0.01), and remained unchanged at 7.29 ± 0.02 during the isoproterenol infusion. The arterial CO₂ tension rose from 30.4 ± 1.0 to 33.7 ± 1.7 mm Hg (p < 0.01) after embolization and did not change during the isoproterenol infusion (PaCO₂ = 33.9 ± 2.2 mm Hg).

**DISCUSSION**

Our studies have shown that the infusion of the pulmonary vasodilator, isoproterenol, does not alter scintigraphic perfusion defects caused by pulmonary emboli in the dog. This was clearly the case for 67% of the 34 defects noted following embolization. The fact that 11 of the defects showed partial or total reperfusion after 30 min of isoproterenol infusion might appear incompatible with this common situation.

---

**TABLE 1. SCINTIGRAPHIC PERFUSION DEFECTS AFTER-EMBOLIZATION AND DURING ISOPROTERENOL INFUSION**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Defects after embolization*</th>
<th>Extent of reperfusion during isoproterenol infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>RL</td>
<td>RL</td>
</tr>
<tr>
<td>2</td>
<td>LL</td>
<td>LL</td>
</tr>
<tr>
<td>3</td>
<td>RL</td>
<td>RL</td>
</tr>
<tr>
<td>4</td>
<td>LU</td>
<td>LU</td>
</tr>
<tr>
<td>5</td>
<td>RU, RM, RL</td>
<td>RL</td>
</tr>
<tr>
<td>6</td>
<td>RM, LU</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>RU, RL, LM, LL</td>
<td>RL, LL</td>
</tr>
<tr>
<td>8</td>
<td>RM, RL</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>No defect</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>LL</td>
<td></td>
</tr>
<tr>
<td>11†</td>
<td>RU, RM, RL</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>RL</td>
<td>RL</td>
</tr>
<tr>
<td>13</td>
<td>LL</td>
<td>LL</td>
</tr>
<tr>
<td>14</td>
<td>RM, RL</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>LM, LL</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>RU, RL, LU, LL</td>
<td>RU, RL, LU, LL</td>
</tr>
<tr>
<td>17</td>
<td>RU, RL, LL</td>
<td>RU, RL</td>
</tr>
<tr>
<td>18</td>
<td>RL</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>RU, RL, LM, LL</td>
<td>RU, RL, LM, LL</td>
</tr>
</tbody>
</table>

* RU = right upper, LU = left upper, RM = right middle, LM = left middle, RL = right lower, LL = left lower.
† Animal died during isoproterenol infusion.

---

**TABLE 2. HEMODYNAMICS BEFORE AND AFTER EMBOLIZATION AND DURING ISOPROTERENOL INFUSION**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Postembolization</th>
<th>Isoproterenol infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.A. mean pressure (mm Hg)</td>
<td>9.8 ± 0.8</td>
<td>18.5 ± 1.2*</td>
<td>17.5 ± 1.1†</td>
</tr>
<tr>
<td>P.A. wedge (mm Hg)</td>
<td>3.3 ± 0.9</td>
<td>5.4 ± 1.4</td>
<td>6.9 ± 1.2*</td>
</tr>
<tr>
<td>Cardiac output (liter/min)</td>
<td>1.7 ± 0.3</td>
<td>2.6 ± 0.3*</td>
<td>3.6 ± 0.5†</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne·sec·cm⁻⁵)</td>
<td>385 ± 72</td>
<td>448 ± 64</td>
<td>246 ± 24</td>
</tr>
</tbody>
</table>

Mean data ± s.e.m., n = 7, * p < 0.05 vs. control.
† p < 0.01 vs. control.
‡ p < 0.01 vs. after embolization.
§ p < 0.05 vs. after embolization.

---

**TABLE 3. GAS EXCHANGE BEFORE AND AFTER EMBOLIZATION AND DURING ISOPROTERENOL INFUSION**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>After embolization</th>
<th>Isoproterenol infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>97.7 ± 2.8</td>
<td>86.6 ± 6.6</td>
<td>95.6 ± 6.9</td>
</tr>
<tr>
<td>PEO₂ (mm Hg)</td>
<td>38.0 ± 2.8</td>
<td>45.3 ± 2.4*</td>
<td>50.7 ± 2.1*</td>
</tr>
<tr>
<td>Qₐ/Qₗ</td>
<td>0.038 ± 0.005</td>
<td>0.063 ± 0.012</td>
<td>0.086 ± 0.018</td>
</tr>
</tbody>
</table>

Mean data ± s.e.m., n = 7.
* p < 0.05 vs. control.
clusion, however, reperfusion after embolization is also a consequence of thrombus resolution or distal migration. As we have demonstrated previously using the same canine embolic model, there is a 50% reduction in embolic volume within 3 hr of embolic release (1/1). That such events, rather than the effects of isoproterenol, accounted for the 33% incidence of partial or total reperfusion seems validated by the postisoproterenol images. In each of the eight reperfused defects in which we obtained postisoproterenol scans, the partial or total reperfusion persisted despite discontinuance of the isoproterenol. Thus, rapid resolution of some of these fresh emboli, rather than the effects of isoproterenol, fully explain these instances of apparent isoproterenol induced reperfusion.

Emboli in man appear to resolve much more slowly than in this animal model (4), and would rarely be subject to study within 30 min after occurrence. Therefore, reperfusion due to resolution of emboli during isoproterenol infusion is not likely to generate interpretive problems in man; and should it, a postisoproterenol image should be clarifying. These postulates, however, remain to be tested in man.

The failure to reverse perfusion defects due to emboli indicates that such defects in the dog are due to extensive mechanical obstruction rather than vasoconstriction associated with embolism. There is, of course, ample evidence from animal research that humoral agents may promote postembolic pulmonary vascular and airway constriction (15,16). Serotonin (5-hydroxytryptamine), released from platelets, is the most widely studied mediator, but histamine, the prostaglandins, and other vasoactive agents may also play a part (17,18).

Isoproterenol is well recognized as a potent pulmonary vasodilator (19). The work of Halmagyi et al. (20) and of Daly (21) has shown it to be effective in diminishing pulmonary vascular and airway constriction in response to barium sulfate microembolization. In the specific context of massive pulmonary embolization in man, McDonald et al. (22) have reported that isoproterenol infusion resulted in a 43% increase in cardiac output with no significant change in pulmonary arterial mean pressure, reflecting a substantial reduction in pulmonary vascular resistance. Thus the embolized vascular bed does respond to isoproterenol by dilating, and our data confirm this fact. In our animals, with embolization of varying severity, isoproterenol infusion was associated with a marked reduction in the calculated pulmonary vascular resistance. Because improvements in hemodynamic status and/or gas exchange might result from clot resolution independent of the action of isoproterenol, we have confined our analysis to the data obtained only in the animals showing no scintigraphic evidence of reperfusion (i.e., clot resolution). Consequently, we feel that the observed reduction in pulmonary vascular resistance and increase in cardiac output stemmed from the well-recognized pharmacological actions of isoproterenol to dilate the pulmonary vasculature and augment cardiac output.

This increase in cardiac output, coupled with no significant change in PaO₂, resulted in a further elevation in PVO₂ consistent with an improvement in systemic oxygen delivery.

Thus, our data suggest that isoproterenol may have both diagnostic and therapeutic applications in the postembolic situation. Diagnostically, our observations indicate that perfusion scan defects in acute pulmonary thromboembolism result from mechanical obstruction of the pulmonary vascular bed and are not reversible by vasodilatation induced by isoproterenol. This observation contrasts with that in experimental canine pneumonia, in which isoproterenol reversed the perfusion defects (6). Thus, the performance of perfusion scans during isoproterenol should assist in distinguishing perfusion defects due to mechanical obstruction or vascular destruction from those due to vasoconstriction.

Therapeutically, isoproterenol infusion enhanced systemic oxygen delivery, increased cardiac output, and lowered pulmonary vascular resistance—an array of effects that should be beneficial to the postembolic patient. Nevertheless, the known potential for isoproterenol to induce or aggravate existing arrhythmias must be taken into account in any decision regarding its clinical use.

Whether these diagnostic and therapeutic uses of isoproterenol will prove helpful in human embolic disease remains to be seen, although similar hemodynamic findings have been reported in man (22). Our view is that the failure to reperfuse should be of greater specificity in man because thrombus dissolution is less likely to compromise interpretation of reperfusion. Failure to reperfuse should be a reliable indicator of pulmonary vascular obstruction or destruction.

ACKNOWLEDGMENTS

Grant support was provided by NIH Fellowship F-32 HL05357 and UCSD Thrombosis Program Project HL18576.

REFERENCES

3. Moser KM, Miale A, Jr: Interpretive pitfalls in lung pho-
12. KELMAN GR, NUNN JF: Nomograms for correction of blood $P_{aO_2}$, $P_{aCO_2}$, pH and base excess for time and temperature. J Appl Physiol 21: 1484-1490, 1966

**NEW ENGLAND CHAPTER**
**THE SOCIETY OF NUCLEAR MEDICINE**
**FALL MEETING**

**Oct. 13-14, 1979**

**Downtown Howard Johnsons**
**Boston, Massachusetts**

The New England Chapter of the Society of Nuclear Medicine announces its Fall Meeting to be held Oct. 13-14, 1979, at the Downtown Howard Johnsons in Boston, Massachusetts.

Topics for lectures to be presented on Saturday include: a) Differential diagnosis of bone lesions, b) Early detection of gastrointestinal bleeding, c) Liver disease and biliary imaging, and d) Pediatric osteomyelitis and genito-urinary reflux. Workshop sessions will be concerned with Bone, Heart, Pediatrics, and Techniques.

On Sunday, following the presentation of the Blumgart Award to Dr. David Kuhl, there will be a symposium on “Tomographic Imaging.”

For further information contact:

Dr. H. William Strauss
Dept. of Radiology
Div. of Nuclear Medicine
Massachusetts General Hospital
Boston, MA 02114

Volume 20, Number 9