Treatment of Canine Embolic Pulmonary Hypertension With Recombinant Tissue Plasminogen Activator

Efficacy of Dosing Regimes

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We investigated effects of two dosing regimes of recombinant tissue plasminogen activator (rt-PA) and sodium heparin on pulmonary thrombolysis in a canine model of pulmonary hypertension, induced by injection of radioactive blood clots. By continuously counting over both lung fields with a mobile gamma camera, we correlated rate and extent of pulmonary thrombolysis with corresponding pulmonary hemodynamics. Treatment with heparin, over a 3-hour interval, did not result in significant thrombolysis or in a decrease in mean pulmonary artery pressure (PAP). In contrast, rt-PA caused marked pulmonary thrombolysis. While total clot lysis was similar when 1 mg/kg rt-PA was infused over 15 (rt-PA₁₅) or 90 (rt-PA₉₀) minutes (47% and 42%, respectively), rate of lysis during infusion was markedly increased with rt-PA₁₅ (56% vs. 27%/hr, p<0.001). Corresponding to the increased rate of thrombolysis with rt-PA₁₅, relative PAP decrease was greater at 15 and 30 minutes. At 4 hours, PAP decreased most with rt-PA₉₀. However, two of the six dogs given rt-PA₁₅ had an increase in PAP and lung radioactivity 1 hour after rt-PA. This was associated with dislodgement of a previously trapped clot. These results suggest that rt-PA may be appropriate therapy for pulmonary embolism and support further studies designed to optimize dosing regimes. (Circulation 1988;19:214–220)

Recent clinical1-5 and basic6-8 studies have demonstrated the efficacy of recombinant tissue plasminogen activator (rt-PA) in inducing thrombolysis. Two prospective, randomized clinical studies demonstrated that rt-PA may be superior to streptokinase in treatment of coronary thrombosis.1,2 In these two studies, while the decrease in systemic fibrinogen levels was greater with streptokinase, bleeding complications, usually at puncture sites, were similar with rt-PA and streptokinase.

While numerous studies have investigated the effects of rt-PA in acute coronary occlusion due to thrombosis, only a few have studied the effects of rt-PA in pulmonary embolism.9,10 The present study was designed to assess the effect of rt-PA on pulmonary thrombolysis in a canine model of radioactive autologous clot embolization. By continuously imaging over both lung fields with a mobile gamma camera, we correlated rate and extent of clot lysis with corresponding pulmonary hemodynamics. Finally, because previous work has suggested that a given dose of rt-PA may be more effective in inducing thrombolysis when given over a short period of time,8 we compared the relative efficacy of rt-PA given over 15 minutes versus the same total dose infused over 90 minutes.

Materials and Methods

Eighteen dogs (15-27.5 kg) were anesthetized with pentobarbital (30 mg/kg i.v.) and supplemented as required to maintain apnea. Each dog was mechanically ventilated in the supine position via an endotracheal tube with 100% O₂ at a tidal volume of 20 ml/kg. Rate was adjusted to maintain PacO₂ between 35 and 45 mm Hg. Metabolic acidosis was treated as required with sodium bicarbonate to maintain arterial pH greater than 7.25. A catheter
was inserted into the right femoral artery. Measurements of blood pressure were obtained from this catheter, and 200 ml blood was drawn for formation of autologous clot. A thermostor-tipped, flow-directed Swan-Ganz catheter (Electro Catheter, Rahway, New Jersey) was inserted via the external jugular vein and positioned in the proximal pulmonary artery. Measurements of cardiac output (CO) and mean pulmonary artery pressure (PAP) were obtained from this catheter. A second Swan-Ganz catheter was placed in the right ventricle to obtain measurements of right ventricular (RV) pressure. A pigtail catheter (Cordis, Miami, Florida) was inserted via the left femoral artery into the left ventricle for measurement of left ventricular end-diastolic pressure (LVEDP). Each catheter was connected to a Statham P23 (Gould, Oxnard, California) transducer leveled to midchest. Transducer output was displayed on a 12-channel Electronics for Medicine oscillograph (PPG Biomedical Systems, Pleasantville, New York).

A third Swan-Ganz catheter was positioned in the right atrium for injection of saline boluses for determination of CO by computer (Columbus Instruments, Columbus, Ohio). An intravenous line, for clot injection, was inserted into the right femoral vein. Figure 1 illustrates the experimental preparation. The surgical procedures were generally completed within 1 hour. During the experiment, normal saline was infused at approximately 100 ml/hr.

Radioactive Autologous Blood Clot Formation

A low specific activity technetium-99m sulfur colloid preparation was created by boiling 3.0 ml 1N HCl, 3.0 ml Na2S2O3·5 H2O, and 1.0–1.5 GBq technetium-99m pertechnetate in 9.0 ml saline for 3.5 minutes. Technetium-99m sulfur colloid (TSC) was chosen to label clot because of its known affinity for fibrin strands and because the small particles (0.1 μm) are rapidly cleared when released by the reticuloendothelial system (serum t1/2 approximately 2 minutes), making background correction unnecessary. After ice-bath cooling for 5 minutes, 0.3 ml human serum albumin and 8.0 ml phosphate buffer were added. High-quality preparations were confirmed with instant thin layer chromatography in methyl ethyl ketone (98.4 ± 0.3%).

Autologous clot was formed by slowly dripping 100 ml freshly drawn unheparinized dog blood with 7.0 ml (350 MBq) TSC and 10,000 units (10 ml) of thrombin into a shielded 500-ml Pyrex beaker. The mixture was allowed to stand for 2 hours until the clot had a “Jello-like” consistency. The serum was decanted and discarded. The low specific activity TSC ensured a large number of particles with adequate distribution in the clot matrix. The use of a small volume of TSC and the glass-walled container were necessary to develop a solid thrombus. The clot was then cut into approximately 1-ml aliquots and loaded into 60-ml syringes before injection.

Protocol

After obtaining baseline measurements, autologous clot was injected via the femoral vein intravenous line and flushed in with normal saline. It was infused gradually over approximately 30 minutes until PAP rose to approximately 55 mm Hg. The dogs were allowed to stabilize for approximately 30 minutes. During this period, there was a small decrease in PAP. After clot injection, hemodynamic measurements were obtained at 10-minute intervals. The preparation was considered stable when measurements of mean blood pressure (BP), CO, and PAP varied less than 10% on two consecutive measurements. After documenting stability, the dogs were then randomly selected for intravenous treatment with bolus sodium heparin at 100 IU/kg (infused over 15 minutes) or rt-PA (Genentech, Toronto, Ontario, Canada) at 1.0 mg/kg given over 15 or 90 minutes through the jugular infusion line. At the beginning of the study, 18 slips of paper each specifying a given treatment (6 rt-PA0, 6 rt-PA90, 6 heparin) were placed in a container. The type of treatment was chosen at the point of randomization by blindly selecting one of these slips. Each treatment was immediately followed with sodium heparin infusion at 10 IU/kg/hr for the remainder of the experiment.

Hemodynamic measurements (BP, PAP, CO, RVEDP, and LVEDP) were obtained and repeated at the following times: baseline, before clot injection; after embolization, immediately before treatment; and at 15, 30, 60, and 90 minutes and 2 and 3 hours after onset of drug infusion.

Assessment of Pulmonary Thrombolysis

Monitoring of lung and abdominal activity was achieved with a Picker Dyra IV mobile gamma counter (Picker International, Winnipeg, Manitoba, Canada) with a parallel hole collimator coupled to an MDS A2 mobile computer (Medtronic of Canada, Richmond, BC, Canada). Four-hour dynamic acqui-
sition was in a 64 × 64 matrix at a 120 sec/frame rate. Thus, an image was obtained every 2 minutes over the course of the experiment. Regions of interest were placed about the lung fields and liver. To assess total pulmonary thrombolysis, counts in the lungs were summed over the 10 minutes just before administration of therapy and were compared with a decay-corrected image from the final 10 minutes. To assess rate of pulmonary thrombolysis, the pulmonary time-activity curves were normalized to the maximum counts in the lung fields that always occurred near the end of the clot infusion. After obtaining the decay-corrected time-activity curve, a marker was placed at the onset and the end of drug infusion, and both linear and exponential best-fit curves between these coordinates were generated by the computer. Because there was no significant difference in description of the data by either equation, a linear model was chosen. The mean ± SD correlation coefficients in dogs treated with rt-PA15, rt-PA90, and heparin were 0.98 ± 0.02, 0.98 ± 0.02, and 0.89 ± 0.03, respectively. Thus, a "slope" of the time-activity curve could be defined to estimate the rate of clot lysis during drug infusion. This relation is expressed in terms of the percent decline of total lung counts per hour. In one dog that received rt-PA over 90 minutes, because of dog and/or camera movement during infusion, we were unable to determine the slope of the time-activity curve. However, total pulmonary thrombolysis was assessed in this dog.

In both rt-PA-treated groups, the final hour of clot lysis closely approximated treatment with heparin alone. To determine when the effects of rt-PA were clearly separate from that of heparin, a line representing the mean rate of clot lysis for heparin was back projected on each experimental line. The point at which the rt-PA line approached within 2 SD of the heparin control line was taken as the point at which clot lysis due to rt-PA ceased.

**Data Analysis**

The total clot lysis, rate of clot lysis during infusion, and time of clot lysis after infusion were compared between groups by a one-way ANOVA. If this were significant (p<0.05), Student-Newman-Keuls test was used to determine which means differed. Hemodynamic parameters were analyzed for change with embolization and change with time after onset of treatment by a two-way ANOVA. These hemodynamic measurements, plus the change in PAP from infusion onset, were compared between groups at each time interval by a one-way ANOVA. If any one-way or two-way ANOVA were significant (p<0.05), Student-Newman-Keuls test was used to determine which points were different.

**Results**

Table 1 illustrates mean hemodynamic values before and after embolization for all 18 dogs. Embolization was associated with a marked increase in PAP (p<0.0005) and RVEDP (p<0.001) and a decrease (p<0.001) in CO. BP and LVEDP remained constant with embolization.

Table 2 illustrates individual and mean effects of heparin, rapid administration of rt-PA (rt-PA15), and short-term infusion of rt-PA (rt-PA90) on rate of clot lysis. The rate of clot lysis observed during treatment and the values obtained after rt-PA was dis-

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**Table 1. Hemodynamic Effects of Embolization**

<table>
<thead>
<tr>
<th></th>
<th>BP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>CO (l/min)</th>
<th>RVEDP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before embolization</td>
<td>137 ± 4</td>
<td>13.9 ± 0.5</td>
<td>3.2 ± 0.3</td>
<td>3.8 ± 0.5</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>After embolization</td>
<td>128 ± 4</td>
<td>45.4 ± 1.0*</td>
<td>2.0 ± 0.2†</td>
<td>7.5 ± 1.2†</td>
<td>5.0 ± 0.5</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

BP, blood pressure; PAP, pulmonary artery pressure; CO, cardiac output; RVEDP, right ventricular end-diastolic pressure; LVEDP, left ventricular end-diastolic pressure.

*p<0.0005, †p<0.001, ‡p<0.01.

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**Table 2. Rate of Pulmonary Thrombolysis**

<table>
<thead>
<tr>
<th></th>
<th>Clot lysis (%/hr)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>During treatment</td>
</tr>
<tr>
<td>Heparin-treated</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
</tr>
<tr>
<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>rt-PA15-treated</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>57.6</td>
</tr>
<tr>
<td>8</td>
<td>47.5</td>
</tr>
<tr>
<td>9</td>
<td>52.6</td>
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<td>10</td>
<td>42.1</td>
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<tr>
<td>11</td>
<td>66.6</td>
</tr>
<tr>
<td>12</td>
<td>70.6</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>56.2 ± 4.5*</td>
</tr>
<tr>
<td>rt-PA90-treated</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>16.4</td>
</tr>
<tr>
<td>14</td>
<td>27.4</td>
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<td>15</td>
<td>29.9</td>
</tr>
<tr>
<td>16</td>
<td>37.1</td>
</tr>
<tr>
<td>17</td>
<td>21.8</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>26.5 ± 3.5†</td>
</tr>
</tbody>
</table>

rt-PA15, rapid rt-PA administration; rt-PA90, short-term rt-PA infusion.

*p<0.001 compared with heparin and rt-PA90; †p<0.001 compared with heparin.
TABLE 3. Individual Times in Minutes of Persistent Clot Lysis After Discontinuing rt-PA15 Treatment (Six Dogs) or rt-PA90 Treatment (Six Dogs)

<table>
<thead>
<tr>
<th>rt-PA15</th>
<th>rt-PA90</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>-7</td>
</tr>
<tr>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>58</td>
<td>-23</td>
</tr>
<tr>
<td>105</td>
<td>-5</td>
</tr>
</tbody>
</table>

Mean ± SEM 48 ± 13*

rt-PA15, rapid rt-PA administration; rt-PA90, short-term rt-PA infusion.

*p<0.01 compared with rt-PA90.

continued and the rate of clot lysis became relatively constant are given. In dogs treated with heparin, rate of lysis was minimal and constant over the 3-hour treatment interval. In contrast, rt-PA caused marked pulmonary thrombolysis. As illustrated in Table 2, compared with heparin, rt-PA90 increased the rate of clot lysis (p<0.001) during the 90-minute infusion interval. Shortly after rt-PA was discontinued, there was a marked attenuation in rate of clot lysis. As illustrated in Table 3, before or shortly after rt-PA90 was discontinued, rate of thrombolysis became constant and similar to that in the heparin group.

Compared with the other two groups, rt-PA15 achieved the most rapid (p<0.001) rate of clot lysis. As depicted in Table 2, during infusion, rate of clot lysis with rt-PA15 was twice as great as with rt-PA90 and 20 times greater than with heparin. As with rt-PA90, after rt-PA15 was discontinued, there was a marked decrease in rate of clot lysis. On average, 48 minutes after rt-PA15 was discontinued, the rate of lysis became constant and was similar to that observed with heparin (Table 3). Figure 2 plots typical time-activity curves for each treatment regime. Note the effectiveness of rt-PA in inducing pulmonary thrombolysis. During infusion, rate of clot lysis was relatively constant. Also illustrated in each condition are time-activity hepatic-uptake curves. Note the direct relation between pulmonary thrombolysis and hepatic uptake. Similar relations were noted in each dog. Figure 3 compares images obtained over the 10 minutes just before treatment with the time decay–corrected images obtained over the final 10 minutes. Note the marked difference between the rt-PA regimes and heparin in inducing pulmonary thrombolysis. Figure 4 plots mean ± SEM results and illustrates the effects of heparin and rt-PA on total extent of clot lysis over 3 hours. Compared with heparin, pulmonary thrombolysis was markedly increased with rt-PA (p<0.001). Despite the different rates of pulmonary thrombolysis observed during rt-PA15 and rt-PA90 infusions, extent of clot lysis was similar.

Table 4 depicts mean ± SEM values and illustrates hemodynamic effects of embolization and treatment. In correspondence with increased thrombolysis with rt-PA, pulmonary hemodynamics improved. Note that while CO and LVEDP remained similar between groups over time, PAP decreased in dogs given rt-PA. Corresponding to the initial, rapid rate of pulmonary thrombolysis with rt-PA15, there was a marked decrease in PAP. Compared with heparin and rt-PA90, at 15 (p<0.01) and 30 minutes (p<0.005, p<0.025), PAP decreased most with rt-PA15. Also, at 30 minutes, in a comparison among groups, PAP was significantly less with rt-PA15 than with heparin (p<0.025). From 1 to 3 hours after onset of treatment, the PAP for both rt-PA groups was less than with heparin (p<0.001). From 90 minutes to the end of the study, PAP was less with rt-PA90 compared with rt-PA15 (p<0.01–0.05) and heparin (p<0.001). Also, comparing rt-PA15 with heparin, PAP was less from 30 minutes to 3 hours. In two of the six dogs treated with rt-PA15, pressure increased after an initial decrease in PAP. This increase was associated with clot fragments observed on nuclear images to migrate from the inferior vena cava into the lung. This may explain the slight increase in PAP after 1 hour in this group. Figure 5 plots mean ± SEM PAP in each group as a function of time. As illustrated in Table 3, note the initial rapid decrease in PAP with rt-PA15 and the more gradual decrease with rt-PA90.

As depicted in Table 4, CO remained similar within and between groups over time. In all groups, RVEDP increased with embolization (p<0.01). Compared with heparin where RVEDP remained constant, RVEDP...
decreased in both rt-PA groups from 15 minutes with rt-PA_{15} and from 30 minutes with rt-PA_{90}. Also, comparing among groups, RVEDP was less with rt-PA_{90} than with heparin or with rt-PA_{15} from 90 minutes to 3 hours. Note that before embolization, RVEDP was lower in the rt-PA_{90} group than in dogs randomized to rt-PA_{15}. This may explain the differences in this parameter between the two rt-PA groups from 90 minutes to 3 hours. Values for LVEDP were within the normal range and remained similar within and among groups over time. Similarly, considering within-group comparisons, other than a small decrease in BP at 3 hours in dogs given heparin, this parameter remained relatively stable over time.

All incision sites for catheter placement were left open, and there was no observed difference in estimated blood loss between groups. Also, hematocrit was measured at the beginning and end of each experiment. While the mean values tended to decrease with rt-PA_{15} (-13%) and rt-PA_{90} (-10%) and remained constant with heparin (+4%), these changes were not significantly different (one-way ANOVA).

With respect to gas exchange, there were no differences among groups at any time. With the exception of one dog in the heparin group, values for arterial O_2 tension were always greater than 210 mm Hg.

**Discussion**

This study was designed to assess the efficacy of a new thrombolytic agent, rt-PA, in inducing thrombolysis in a canine model of autologous blood clot pulmonary emboli. Our study also tested the hypothesis that rapid administration of a given dose of rt-PA would result in more complete clot lysis than prolonged administration of the same dose.

We observed that compared with treatment with heparin, rt-PA was efficacious in inducing pulmonary thrombolysis and improving pulmonary hemodynamics. In a comparison among groups treated with rt-PA, while extent of clot lysis was similar with rt-PA_{15} and rt-PA_{90} during infusion, the rate of pulmonary thrombolysis was markedly increased with rt-PA_{15}. Corresponding to the rate of clot lysis, during infusion, PAP decreased most rapidly with rt-PA_{15}. As indicated, none of the treatment regimes caused excessive bleeding. Because the majority of deaths due to right ventricle failure and shock complicating massive pulmonary embolism occur relatively early after onset of symptoms,^{13,14} the therapeutic regime that induces the most rapid pulmonary thrombolysis is probably preferred over regimes that have slower onsets of action.

As discussed in "Results," in two of the six rt-PA_{15} dogs, there was evidence of reembolization and an increase in PAP 1 hour after rt-PA. While this observation may support prolonged infusion of rt-PA in our model, only small numbers are involved, and this may represent an artifact of this preparation. That is, radioactivity was sometimes detected in the inferior vena cava. This must represent trapping of
clot fragments that subsequently dislodged and reembolized in the two dogs discussed above.

The thrombolytic efficacy of rt-PA has previously been demonstrated in both basic and clinical studies. A recent clinical study of patients with acute myocardial infarction reported that for the doses used, rt-PA was twice as effective as streptokinase in inducing acute coronary thrombolysis. Other clinical and basic studies have confirmed the effectiveness of rt-PA in acute coronary thrombolysis. Also, recent studies have reexamined the role of lytic therapy in venous thromboembolism. Experimental studies in animal models and initial case reports and clinical studies indicate that rt-PA may be an excellent drug for treatment of venous thromboembolism.

One study used rabbits to investigate the effects of different dosing regimens of rt-PA on thrombolysis of radioactive jugular vein thrombi. The same dose of rt-PA infused over 15, 30, 60, and 240 minutes produced 96%, 88%, 87%, and 36% thrombolysis, respectively. While the 1-hour infusion of rt-PA increased bleeding and decreased α2-antiplasmin levels, the same dose infused over 15 and 30 minutes did not affect these parameters. The present study describes similar but not identical effects between rt-PA infused over 15 and 90 minutes. While the rate of pulmonary thrombolysis was much greater during rt-PA15 infusion, there was evidence of reembolization in two of the six rt-PA15 dogs, and final extent of lysis was similar between rt-PA15 and rt-PA90. The difference in results between studies may be explained by the obvious differences in experimental design. However, results from both studies suggest that rapid infusion of rt-PA may be the preferred method of administration.

A recent clinical study used rt-PA in treatment of patients with pulmonary embolism. Goldhaber et al treated 36 patients with documented pulmonary embolism. rt-PA (50 mg) was infused over the first 2 hours, followed by angiotherapy and additional rt-PA (40 mg/4 hr) as required. The quantitative score, an index of vascular obstruction, improved 21% by 2 hours and 49% by 6 hours. However, PAP only decreased slightly (p<0.05) after rt-PA therapy, from

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Plot of effects of treatment of mean pulmonary artery pressure, ○, A, and △, treatment of heparin, rt-PA90, and rt-PA15, respectively.
22 to 18 mm Hg, and values for CO were not reported. The relatively small amount of clot lysis that occurred over the first 2 hours may be due to the slow infusion rate of a relatively low dose of rt-PA. The same authors subsequently extended their observations by studying an additional 11 patients with pulmonary embolism.16

In contrast to the study cited above,9 acute and short-term pulmonary thrombolysis were more rapid and more complete in the present study where a larger dose of rt-PA was administered more rapidly. Corresponding to thrombolysis with rt-PA, PAP dramatically decreased. As depicted in Table 3, pulmonary thrombolysis continued for a mean time of 48 minutes after rt-PA was discontinued. Therefore, effective thrombolytic time with rt-PA was approximately 60 minutes. As illustrated in Figure 5, PAP continued to decrease in this group for approximately 1 hour after onset of treatment. Subsequently, when rate of clot lysis was minimal and similar to that observed in heparin-treated dogs, PAP remained relatively constant. If reembolization had not occurred in two dogs, PAP would have been lower. Because the circulating half-life of rt-PA is reported to be short (approximately 5 minutes), these results suggest protection of both fibrin-bound rt-PA and plasmin from their inhibitors. A study using rabbits also reported sustained lysis of radioactive jugular vein thrombi after bolus injection of rt-PA.7 In contrast to the 15-minute infusion of rt-PA, the rate of clot lysis and change in PAP became similar to the heparin group when the infusion of rt-PA ceased in dogs given rt-PA over 90 minutes. In those dogs treated with heparin, there was trivial thrombolysis and PAP remained relatively constant over the 3-hour treatment interval. The failure for CO to increase in dogs treated with rt-PA may be explained by relative hypovolemia. That is, while RVEDP remained elevated in dogs treated with heparin, this parameter decreased in those given rt-PA.

While there is some debate, most physicians agree that when circulatory compromise complicates pulmonary embolism, thrombolytic therapy may be indicated. Results from the present study and those cited above suggest that rt-PA may be an excellent drug for treatment of pulmonary thromboembolism. Further, results from the present study indicate that the method of administration of rt-PA may significantly affect the dynamics of thrombolysis. We emphasize caution in extrapolation of our results to the clinical area because these findings were in an anesthetized canine preparation with exogenously produced autologous blood clots. However, these results support further prospective studies designed to optimize dosing regimens of rt-PA.

References


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