Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism


ABSTRACT Eight centers participated in a study in which intrapulmonary and intravenous administration of recombinant tissue-type plasminogen activator (rt-PA) were compared in 34 patients with acute massive pulmonary embolism. All patients received intravenous heparin in a bolus of 5000 IU followed by 1000 IU/hr. After 50 mg rt-PA given over 2 hr the severity of embolism, determined from pulmonary angiograms, declined by 12% in the intrapulmonary drug group (p < .005) and 15% in the intravenous drug group (p < .005); mean pulmonary arterial pressure fell from 31 ± 7 to 22 ± 6 mm Hg (p < .005) and from 31 ± 12 to 21 ± 9 mm Hg (p < .005) in the respective groups. After a further 50 mg given over 5 hr (22 patients), the angiographically determined severity of embolism had decreased by 38% from baseline in the intrapulmonary drug group and by 38% in the intravenous drug group. The mean pulmonary arterial pressure further declined to 18 ± 7 and 12 ± 5 mm Hg in the respective groups. Fibrinogen levels dropped to 48% of baseline after 50 mg and to 36% of baseline after 100 mg rt-PA. Some degree of bleeding at puncture and/or operation sites was noted in 16 patients, including four who required a transfusion of two or more units of blood and had been operated on an average of 7.5 days (range 2 to 13) before thrombolytic treatment was started. In seven other patients thrombolytic treatment was initiated an average of 8.5 days (range 3 to 15) after surgery and only very minor or no bleeding was observed. This trial indicates that the intrapulmonary infusion of rt-PA does not offer a significant benefit over the intravenous route and suggests that a prolonged infusion of rt-PA over 7 hr (100 mg) is superior to a single infusion of 50 mg over 2 hr.


A NUMBER of studies1-13 has demonstrated the accelerated resolution of pulmonary emboli that can be obtained with thrombolytic therapy and in 1980 a National Institutes of Health consensus conference14 concluded that "...ideal therapy for pulmonary embolism requires either the surgical removal or lysis of the thrombus or embolus." Despite the established superiority of thrombolytic over heparin treatment for hemodynamically compromised patients with massive pulmonary embolism, such therapy has not been universally adopted and there remains a significant group of patients to whom thrombolytic agents are not given. Such patients include those in whom the risk of bleeding induced by streptokinase or urokinase is thought to outweigh the benefit, particularly postsurgical patients, and those in whom embolism is so massive that death supervenes, or is thought likely to supervene, before thrombolysis can start to reverse the hemodynamic disturbance. Thus, despite the availability of potent agents such as streptokinase and urokinase, the search for better thrombolytic drugs continues. A thrombolytic agent with a minimal systemic fibrinogenolytic effect and fast action on the thrombus would be particularly desirable. The recent development of recombinant tissue-type plasminogen activator (rt-PA), a newer thrombolytic agent with relative fibrin specificity and fibrinogen-sparing properties,15 has provided physicians with a potent agent that has the promise of fulfilling at least some of these requirements.

The effect of rt-PA in improving vessel patency in acute myocardial infarction has been investigated in several multicenter trials.16-20 The present pilot study was designed to answer several questions. (1) Is an intravenous infusion of rt-PA as effective as an intrapulmonary infusion in the treatment of acute massive
pulmonary embolism? (2) Can a dose of 50 mg rt-PA reverse the hemodynamic disturbance and clear the major portion of the angiographically visualized emboli, or is twice this dose required? (3) What is the magnitude of the undesirable systemic effect and its associated risks?

Reported here are the results of a study, carried out at eight European centers,* of rt-PA in patients with massive pulmonary embolism.

Methods

Subjects. Patients admitted to the trial fulfilled the following inclusion criteria: (1) Clinical signs and symptoms indicative of pulmonary embolism within 5 days of onset and a confirmatory pulmonary angiogram showing vascular obstruction greater than 48% (angiographic score ofseverity > 15).2 (2) Age range between 21 and 75 years. (3) Patient willingness and ability to give informed consent for the proposed treatment regimen. In addition, the study protocol had to have approval from the local ethics committee.

Study protocol. Patients were excluded if they met any of the following criteria: pregnancy, thoracic or neurosurgery performed at any time, other major surgery performed in the last 72 hr, a history of cerebrovascular accident in the last 6 months, known uncontrolled hypertension (defined as >120 mm Hg diastolic pressure before occurrence of the pulmonary embolism or at the time of contemplated rt-PA infusion), major head injury in the last month, major hepatic or renal disease, known active peptic ulcer or bleeding disorder.

The procedure for pulmonary angiography as routinely used in the cooperating clinical centers was followed with the exception that the internal jugular vein or subclavian vein was not used; an anionic contrast medium was selected and standard cut or cine angiography (main stream, right and left pulmonary artery) were required.

After confirmation of diagnosis by pulmonary angiography, the route of rt-PA administration, intravenous or intrapulmonary, was determined by telephone randomization; rt-PA was then given as a bolus of 10 mg followed by 20 mg/hr over the first 2 hr (dose 50 mg). All patients received intravenous heparin in a bolus dose of 5000 IU followed by 1000 IU/hr by constant-rate infusion pump.

Pulmonary angiography was repeated at the end of the 2 hr infusion period. The severity of embolism was assessed initially by the physician responsible for treatment by the method of Miller et al.2 The system provides a score of from zero to 34, made up of a maximum of 16 for the thrombus itself and 18 for the peripheral perfusion defect as assessed by lack of opacification of the peripheral vessels by contrast medium. Massive embolism was judged to be present if the score was 15 points or more. When the responsible physician assessed the score as 15 points or more after 2 hr of treatment, a second infusion of 50 mg rt-PA was given over 5 hr by the same route of administration. In such cases, a third pulmonary angiogram was obtained between 7 and 18 hr from the start of the initial infusion and the infusion of heparin was continued until this third angiogram. This window was allowed so that the third pulmonary angiogram could be recorded during usual working hours. Further treatment with heparin after the second or, when performed, third angiogram was at the discretion of the individual physician. The administration of thrombolytic agents other than rt-PA and any form of surgery after the last pulmonary angiogram had to be reported.

The pulmonary angiograms were subsequently centrally reviewed by an independent panel of five radiologists who were unaware of the chronologic order of the angiograms and the route of administration of rt-PA. The individually allocated scores were reviewed and a consensus score was derived. The final consensus scores allocated to the angiograms are reported below.

Arterial blood pressure (sphygmonanometer), pulse rate, and respiratory rate were recorded on admission (baseline) and just before, during, and immediately after the first and (if given) second infusion of rt-PA. Hemodynamic measurements (right atrial, right ventricular, and pulmonary arterial pressure, pulmonary arterial oxygen saturation, hemoglobin, and hematocrit) were measured just before starting treatment and at the end of the first infusion. In cases in which a second infusion of rt-PA was given, these measurements were repeated just before the start and on completion of the second infusion.

Blood samples for study of the coagulation and fibrinolytic systems were taken at the same time intervals as mentioned above and 30 min after the last rt-PA infusion. Two tubes were provided for each blood collection, one containing 0.5 ml sodium citrate (final concentration 0.01 mol/l) and the other citrate and aprotinin (final concentration 150 KIU/ml) to counteract proteolysis generated by plasmin in vitro. A total of 4.5 ml of blood was collected in each tube and centrifuged within 1 hr, and the plasma was stored at −20°C. Fibrinogen was determined by means of a clotting-rate assay.21 Fibrin degradation products (FDP)22 and rt-PA antigen were also measured.23 Assays were performed by a central laboratory in Leuven, Belgium.

rt-PA was produced by Genentech, Inc., and supplied by Boehringer Ingelheim, GmbH; the preparation used (G 11044) contained mainly single-chain rt-PA.

Statistical analysis. All results are expressed as the mean ± SD. Intragroup statistical analysis was performed with a paired t test or a signed rank test, depending on the normality of the distribution of the data. Normality was evaluated with the Shapiro-Wilke statistic; the threshold value was p = .10. Intergroup statistical analysis was performed with the use of the differences between the values after the first infusion of rt-PA and baseline values. The overall effect and the group effect was evaluated with a one-way analysis variance. The percentages of patients requiring a second infusion in each treatment group were compared with chi-square test corrected for continuity. All calculations were made with the statistical package SAS.24

Results

Angiographic and hemodynamic findings. Patients were admitted to the study and randomly assigned to two treatment groups: the intrapulmonary (19 patients) and intravenous infusion (15 patients) groups. The baseline characteristics of the patients are listed in table 1. The only protocol violation was a patient admitted to the trial 40 hr after cholecystectomy (data from this patient are included in the analysis). More patients with recent surgery (15 days or less) received intrapulmonary rt-PA (eight of 19, compared with four of 15 patients randomly assigned to intravenous rt-PA).

Analysis of the angiograms by the reviewing panel indicated that the pulmonary angiographic severity score had fallen from 25 ± 3 to 22 ± 7 points in the

*Participating centers and study administrators are listed before the references.
TABLE 2

Hemodynamic variables and pulmonary angiographic scores of severity during and after thrombolytic treatment

<table>
<thead>
<tr>
<th>rt-PA infusion</th>
<th>Blood pressure (mm Hg, mean ± SD)</th>
<th>Pulse rate (bpm, mean ± SD)</th>
<th>Respiration rate per min (mean ± SD)</th>
<th>Mean pulmonary arterial pressure (mm Hg, mean ± SD)</th>
<th>Pulmonary artery O₂ saturation (%)</th>
<th>Pulmonary angiographic score of severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before infusion</td>
<td>19</td>
<td>118 ± 28</td>
<td>77 ± 18</td>
<td>102 ± 21</td>
<td>29 ± 9</td>
<td>31 ± 7</td>
</tr>
<tr>
<td>After 1st infusion</td>
<td>19</td>
<td>126 ± 19</td>
<td>78 ± 10</td>
<td>95 ± 15B</td>
<td>23 ± 5B</td>
<td>22 ± 6B</td>
</tr>
<tr>
<td>After 2nd infusion</td>
<td>14</td>
<td>122 ± 27</td>
<td>79 ± 13</td>
<td>92 ± 15</td>
<td>19 ± 3E</td>
<td>18 ± 7C</td>
</tr>
<tr>
<td>IV group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before infusion</td>
<td>15</td>
<td>128 ± 21</td>
<td>86 ± 12</td>
<td>106 ± 22</td>
<td>31 ± 9</td>
<td>31 ± 12</td>
</tr>
<tr>
<td>After 1st infusion</td>
<td>15</td>
<td>125 ± 13</td>
<td>85 ± 8</td>
<td>97 ± 27</td>
<td>28 ± 8</td>
<td>21 ± 9A</td>
</tr>
<tr>
<td>After 2nd infusion</td>
<td>8</td>
<td>121 ± 15</td>
<td>84 ± 5</td>
<td>85 ± 13</td>
<td>22 ± 5D</td>
<td>12 ± 5C</td>
</tr>
</tbody>
</table>

PA = intrapulmonary drug; IV = intravenous drug.

*p < .05; **p < .005: significance of differences between values before and after first infusion.

*p < .05; **p < .01; ***p < .005: significance of differences between values after first and second infusion.
normalized by the end of the second infusion at a mean elapsed time of 9 hr.

Two patients received, after the second infusion of rt-PA, subsequent thrombolytic treatment. In one patient urokinase was given because the pulmonary angiographic severity score had only decreased from 22 to 14; in the other patient the severity score had remained 21 and a streptokinase infusion was given over 3 days. No control pulmonary angiogram was obtained after treatment with urokinase or streptokinase.

Hematologic results. The hematologic results are listed in table 3. The hematocrit remained unchanged during thrombolytic treatment. Disregarding the route of administration of rt-PA, plasma fibrinogen decreased from 3.87 g/liter before treatment to 2.06 g/liter after the first infusion in all patients (−47%) and from 3.91 to 1.36 g/liter after the second infusion in the

FIGURE 1. Individual data for and mean (± SD) respiration rate, pulmonary arterial pressure, pulmonary artery O₂ saturation, and pulmonary angiographic score of severity in patients with acute massive pulmonary embolism treated with one or two infusions of rt-PA administered in the pulmonary artery (PA) or in a systemic vein (IV).
TABLE 3
Hematologic variables before, during, and after thrombolytic treatment with rt-PA

<table>
<thead>
<tr>
<th>rt-PA infusion in pulmonary artery</th>
<th>Hematocrit (% of all patients)</th>
<th>Fibrinogen (g/l)</th>
<th>FDPs (μg/ml)</th>
<th>t-PA antigen (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before infusion</td>
<td>39.2 ± 0.7</td>
<td>4.27 ± 0.8</td>
<td>13 ± 8</td>
<td>7.1 ± 2</td>
</tr>
<tr>
<td>After 1st infusion</td>
<td>37.6 ± 0.7</td>
<td>2.52 ± 1.3</td>
<td>256 ± 363</td>
<td>742 ± 356</td>
</tr>
<tr>
<td>After 2nd infusion</td>
<td>39.5 ± 0.5</td>
<td>1.36 ± 1.1</td>
<td>404 ± 544</td>
<td>255 ± 139</td>
</tr>
</tbody>
</table>

rt-PA infusion in systemic vein

| Before infusion                   | 39.5 ± 0.3                   | 3.36 ± 0.1      | 44 ± 55      | 10.8 ± 6            |
| After 1st infusion                | 39.7 ± 0.4                   | 1.48 ± 1.1      | 405 ± 420    | 678 ± 34            |
| After 2nd infusion                | 39.5 ± 0.3                   | 1.35 ± 0.8      | 471 ± 698    | 226 ± 118           |

patients treated with 100 mg rt-PA (−65% from baseline levels). The fibrinogen level fell below 1 g/liter in five patients; the largest individual decline in fibrinogen level was −91%.

Serum FDPs increased from 27 μg/ml at baseline to 322 μg/ml after the first infusion in all patients and from 21 μg/ml at baseline to 428 μg/ml in the patients treated with 100 mg rt-PA. Mean rt-PA antigen levels were 9.4 ng/ml before and 714 ng/ml at the end of the first infusion of 50 mg rt-PA administered over 2 hr. The starting level of rt-PA antigen in patients receiving two rt-PA infusions was 11 ng/ml, after the first 2 hr infusion it was 726 ng/ml, and at end of the second infusion of the same dose over 5 hr it was 245 ng/ml. No significant difference was observed in changes in fibrinogen, FDPs, or rt-PA antigen levels in the intrapulmonary drug and the intravenous drug groups.

Mortality and morbidity. There were two deaths. One patient, a 63-year-old woman, suffered a massive pulmonary embolus 2 weeks after nephrectomy. Cardiac arrest occurred 5 hr after the onset of symptoms and again 15 min after starting rt-PA treatment. She could not be resuscitated from this second cardiac arrest. The second patient, a 61-year-old woman, still had a high angiographic severity score at the end of the second rt-PA infusion. Pulmonary embolectomy was performed 10 hr later, but the patient died from extensive intrapulmonary hemorrhage after coming off bypass. The physician in charge reported that 20,000 instead of 2000 IU heparin was inadvertently injected intravenously 6 and 8 hr after the start of the first rt-PA infusion.

Some degree of bleeding was noted in 16 patients, five of whom had undergone recent surgery (mean 8.6 days, range 2 to 13). In most instances bleeding occurred at puncture and/or operation sites. Hematemesis (not requiring blood transfusion) occurred in one patient and epistaxis (for which 1 unit of blood was given) was noted in another. In four of these 16 patients more serious bleeding occurred that required transfusion of 2 or more units of blood; these four patients had been recently operated upon (mean 7.5 days, range 2 to 13). Bleeding started at the operation site 7 days after surgery for a femoral fracture (one patient) and for hip replacement (one patient). Bleeding from a previously unknown peptic ulcer was noted in a patient who was treated for pulmonary embolism occurring 13 days after bilateral knee replacement. The fourth patient bled from the nasopharynx and through the operation drain when treated with rt-PA 40 hr after cholecystectomy (protocol violation). This patient suffered two cardiac arrests before being treated with rt-PA. She received a second infusion of rt-PA after a delay of 7 hr and excessive bleeding was at least partly due to heparin overdose in the preinfusion period. This patient was the only one in whom the hematocrit fell by more than 10 points. She eventually made a complete recovery. In 18 patients, seven of whom had had recent (mean 8.5 days, range 3 to 15) surgery, only very minor or no bleeding was reported.

In three patients a second infusion of rt-PA could not be given. In one patient, because of excessive bleeding at the site of hip replacement performed 7 days earlier, 3 units of blood were transfused (patient accounted for above). In another, nonoperated patient no second infusion was given because of pericardial effusion that did not require aspiration that was discovered on the second pulmonary angiogram. A successful pulmonary embolectomy was performed in a third patient 6 hr after the end of the first rt-PA infusion because the pulmonary angiographic score did not decrease; no bleeding problems were observed during or after the surgical procedure.

Discussion

The present study demonstrates that rt-PA, in a dose of 100 mg administered intravenously or into the pul-
monary artery over a 7 hr period, results in significant lysis of massive pulmonary emboli. A concordant conclusion was reached by Goldhaber et al., 25 who studied the effect of intravenous rt-PA in similar doses in 36 patients with angiographically documented pulmonary embolism. In the latter study unilateral pulmonary arteriograms were used and patients in shock (systolic arterial pressure <80 mm Hg) were excluded. All of the patients reported in the present study had massive embolism and all had documented bilateral pulmonary emboli. The frequency of intense dyspnea and high mean pulmonary arterial pressure indicated the clinical severity of embolism; pretreatment systolic blood pressures of less than 100 mm Hg were documented in seven patients. Two of the patients had each suffered two cardiac arrests, leading to death in one.

That thrombolysis can be achieved is not surprising; the effect of both streptokinase and urokinase in lysing pulmonary emboli, and their superiority over heparin, have been demonstrated many times in the past. 1-13 That rt-PA is equally effective by the intravenous and by the intrapulmonary route of administration could be expected but had to be demonstrated because no studies have been reported comparing intravenous with intrapulmonary administration of lytic agents in acute pulmonary embolism. That the intrapulmonary route is equally effective has considerable practical importance.

The finding of this trial that 100 mg was more effective than 50 mg, although very likely, needs to be interpreted with some caution. It is possible that a single, 2 hr infusion of 50 mg rt-PA, although having little effect at 2 hr, might have produced continuing lysis resulting in a 7 to 18 hr end point similar to that achieved by a 100 mg infusion lasting 7 hr. This possibility is of importance since the most impressive result of the study was that significant lysis, approximately 50%, was achieved within an 8 hr period (with a maximum period of 18 hr). This degree of lysis is comparable to that obtained with a 24 hr infusion of streptokinase or urokinase 5 and to that seen 24 hr after a 12 hr infusion of urokinase. 3 We know of no study in which the effect of urokinase or streptokinase has been assessed angiographically at 7 to 18 hr but it is equally possible that the major effect of these two agents is achieved much earlier than our chosen study end point.

Petitpretz et al. 26 noted that in seven continuously monitored patients treated by a bolus injection of 15,000 IU of urokinase per kilogram, the greatest part of the total hemodynamic improvement occurred within the first 3 hr after injection. Similar observations have been reported by others. 27, 28 In the present study hemodynamic variables were measured at 2 hr and again after the second treatment period (7 hr). Table 2 reveals a significant improvement at 2 hr with further amelioration after 7 hr. The ideal hemodynamic measurement is total pulmonary resistance. It is the true measure of the effect of lytic therapy; arteriography tends to underestimate the degree of improvement since the score makes no allowance for a reduction in the size of emboli other than that reflected by any consequent improvement in flow. 2 Pulmonary resistance measurements were not available to us because we did not have direct measurements of cardiac output. The effect of a falling resistance on pulmonary arterial pressure will be partially obscured by a concomitant rise in cardiac output. In the present study we derived a “resistance index” by dividing the mean pulmonary arterial pressure by the pulmonary artery O2 saturation. This resistance index fell at 2 hr from 0.59 to 0.40 and decreased further to 0.22 at 7 hr after the start of treatment.

There remains a question of the magnitude of the systemic effect of rt-PA that accompanied lysis of emboli and of the incidence and severity of bleeding complications. It is clear that rt-PA is only relatively fibrin selective since fibrinogen levels declined to 36% of baseline after 100 mg rt-PA. In the Urokinase Pulmonary Embolism Trial (UPET), a loading dose of 2000 CTA units/pound of body weight was given followed by the same dose per hour for 12 hr. 3 The average fall in fibrinogen was 49% of the starting value. In the UPET trial the definition of major bleeding was a fall in hematocrit greater than 10 points or necessity for a transfusion of more than 2 units of blood. By the same criteria, the incidence of major bleeding in the present study was 12% (4/34), as compared with an incidence of 27% in phase 1 of UPET 5 and 12% in phase 2. 5 These four patients had had a major operation a mean of 7.5 days (range 2 to 13) before treatment with heparin and rt-PA. The fibrinogen level in three of them remained above 1.5 g/liter (in the fourth patient the lowest value was 0.5 g/liter), suggesting that lysis of hemostatic fibrin plugs by rt-PA or some other mechanism rather than a low fibrinogen level are related to bleeding. The UPET trial 3 was conducted between 1968 and 1970, at a time when blood transfusions were more readily given than they are now; moreover, the UPET study required more diagnostic phlebotomy than the current rt-PA study and this may in part explain the greater decline in hematocrit among the urokinase-treated patients in UPET.

That only two patients died, one after embolectomy, in a group with massive pulmonary embolism, accompanied by shock in many cases, is noteworthy. How-
ever, since clinical experience suggests that the risk of death of a patient with massive pulmonary embolism is remarkably low once the patient has survived the first few hours, it will be extremely difficult to demonstrate a reduction in mortality with thrombolytic agents used after this time interval.3,5

This pilot trial indicates that intrapulmonary infusion of rt-PA does not offer significant benefit over the intravenous route and suggests that a prolonged infusion of rt-PA over 7 hr (100 mg) is superior to a single infusion of 50 mg over 2 hr. Lysis of emboli in large pulmonary vessels began in the first 2 hr after starting treatment, but pulmonary arterial pressure did not normalize until a total of 7 hr of rt-PA treatment had been given. A larger trial is needed to further define the speed of action and the minimal effective dose of rt-PA as compared with those of other, established, thrombolytic agents used for therapy of acute massive pulmonary embolism.

We are grateful to Mr. E. Lesaffre, Division of Medical Informatics, Faculty of Medicine, University of Leuven, Belgium, for his expert help with the statistical analysis.

Study centers and personnel


Participating clinical centers: Kantonsspital, Basel (F. Duckert, G. Marbet, H. E. Schmitt), Hôpital Cantonal Universitaire, Genève (B. Krähenbühl, H. Bounameaux, P. A. Schneider, Ph. de Moerloose); Universitair Ziekenhuis Gasthuisberg, Leuven (M. Verstraete, J. Vermynen, D. Collen, R. Verhaeghe, M. Pombaerts); Brompton Hospital, London (G. A. H. Miller); University Hospital of Lund (C. G. Olsson, R. Nilsson, A. Sjögren, M. Olofsson); Groupe Hospitalier Régional et Universitaire, Marseille (A. Serradimigni, G. Lecorff, J.-L. Bouvier); Centre Hospitalier Régional de Bordeaux, Pessac (P. Besse, H. Bricaud, J. P. Colle); Centre Hospitalier Régional et Universitaire de Tours, Tours (M. Brochier, B. Charbonnier, L. F. Garnier).

References

Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism.
M Verstraete, G A Miller, H Bounaumeaux, B Charbonnier, J P Colle, G Lecorf, G A Marbet, P Mombaerts and C G Olsson

Circulation. 1988;77:353-360
doi: 10.1161/01.CIR.77.2.353

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/2/353

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/