fluoroscopy time, which is under control of the operator, as a primary outcome measure. Although not ideal, it allowed us to make a meaningful estimate of the number of patients who would need to be included in the study. It is possible that we might have overcome the variability by completing a much larger study, but we wanted to focus on those factors that might be easily modifiable by the operator.

We did not find a difference in the kerma-area product in our study groups despite a difference in fluoroscopy time. Dr. Miller speculates that we might have collimated to half the field in those cases in which unilateral embolizations were performed, and this would explain the failure to find a difference. We did not, in fact, consciously do that. We routinely collimated the field during the embolization to the uterus and the very immediate adnexa, and we did not vary it consciously when performing a unilateral or bilateral embolization. Although we likely increased collimation somewhat during the unilateral procedures, we did not measure the difference and doubt it was as much as 50%. This is because the vessels on one side can supply leiomyomas across the midline, and it is also possible to have arteriovenous shunting on either side near the end of the procedure. Arteriovenous shunting is one sign of the appropriate endpoint of embolization, and we believe it is important to monitor it.

We believe that it is more likely that the variability of body habitus, uterine size, and uterine location were greater than the estimated difference in the measured fluoroscopy time and imaging. This was shown in the earlier study by Bratby et al (1) we referenced in our study. They used an anthropomorphic phantom and simulated unilateral and bilateral procedures based on values from their study. They did find a difference in dose-area product and cumulative dose when body size factors were held constant (1). We did not repeat that confirmation, as we did not have sufficiently detailed data to duplicate a typical procedure. For example, we did not record the time of anteroposterior fluoroscopy, fluoroscopy time with tube angulation, the degree of tube angulation, or the average collimation dimensions.

We still believe that, all other things being equal, less fluoroscopy and imaging use are likely to reduce patient exposure, and this reduction cannot be completely mitigated by more aggressive collimation in uterine artery embolization procedures. The need to provide adequate monitoring of the procedure prevents a perfect trade-off of fluoroscopy time and field collimation. Having said that, limiting the tissue area exposed is an important component of radiation-safe practice, and we thank Dr. Miller for raising the issue.

Mary Costantino, MD
Justin Lee, MD
Michael McCullough, MD
Hala Nsouli-Maktabi, MPH, and
James B. Spies, MD
Department of Radiology
Georgetown University Medical Center
CG 201, 3800 Reservoir Road NW
Washington, DC 20007-2113

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Angiojet Rheolytic Thrombectomy in Massive Pulmonary Embolism: Locally Efficacious but Systemically Deleterious?

From: Robert F. Bonvini, MD
Marc Righini, MD
Marco Roffi, MD
Cardiology Division (R.F.B., M.Roffi), and Angiology and Hemostasis Division (M.Righini)
University Hospital of Geneva
4, Rue Gabrielle Perret-Gentil
1211 Geneva 14/Switzerland

Editor:

We congratulate Kuo et al (1) for their landmark meta-analysis of the recent studies on feasibility, safety, and efficacy of percutaneous mechanical thrombectomy (PMT) in massive pulmonary embolism (PE). We agree with the conclusion of the authors that in the near future, PMT may become first-line therapy for patients with massive PE, especially in the presence of contraindications to systemic intravenous thrombolysis. As pointed out in the article, larger studies are needed, however, to define the exact role of PMT—alone or in combination with low-dose in situ thrombolysis—in this life-threatening condition.

Currently, several PMT devices are available, but for all of them massive PE is considered an off-label indication. Most of the devices have been studied only in small retrospective series and were used in highly selected patient groups. The mean age of 53 years described in these meta-analyses by Kuo et al suggests that elderly—and likely sicker—patients have been largely excluded from the studies. This observation also may partly explain the high (87%) procedural success rate—defined as stabilization of hemodynamics, resolution of hypoxia, or survival to hospital discharge—which is far more favorable than the outcomes described in most reports on massive PE reports (2). Another explanation for these findings is the inclusion in most of the studies of patients with submassive PE. Accordingly, the series of Chechi et al (3) comprising 51 patients treated with rheolytic thrombectomy describes an overall in-hospital mortality rate of 16%, whereas patients with true massive PE had a mortality of 43%. Based on these observations, the assessment of safety and efficacy of modern PMT devices in massive PE remains challenging.

For these reasons, at the University Hospital of Geneva, Switzerland, we started in October 2008 a prospective study on the use of Angiojet Rheolytic Thrombectomy (ART) (Possis Medical, Minneapolis, Minnesota) on all consecutive patients presenting with massive PE (Clinical Trial No. NCT00780767). We chose ART over other PMT devices because in vitro and animal tests have suggested that the use of ART in the pulmonary circulation was as effective as other devices while being associated with a smaller risk of device-related complications. Biederer et al (4) showed in an animal model of massive PE that the safety-to-efficacy ratio favored ART compared with two other hydrodynamic devices, especially in vessels with greater than 6 mm diameter.

An important technical feature of ART is that the high-pressure saline jet expulsion at the catheter tip (2500 psi or

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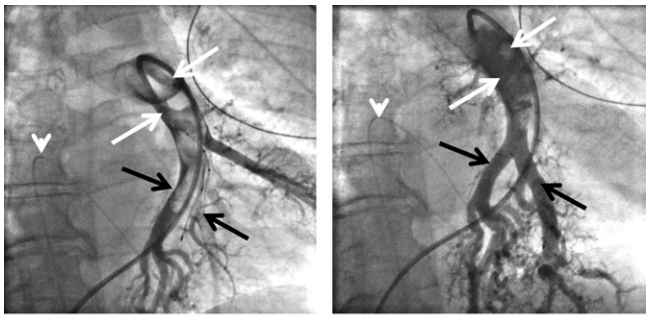
1.7×10^7 Pa) does not seem to injure the vessel wall. When a soft-tip guide wire is positioned in the distal segment of the occluded pulmonary artery and ART is activated, the vacuum effect (ie, Bernoulli effect) produces thrombus fragmentation and aspiration in the absence of vessel damage. Compared with other PMT devices such as the Aspirex (Straub Medical, Wangs, Switzerland) that require placement inside or very close to the thrombus for proper thrombectomy effect, the saline jet expulsion at 360 degrees around the catheter of ART allows for thrombus fragmentation and aspiration even if the catheter is positioned several millimeters away from the thrombus. This property is potentially of major importance because pulmonary artery perforation frequently has a lethal outcome in anticoagulated patients (5).

Several issues probably directly related to ART device activation in the pulmonary circulation may limit the impact of this technique. First, the need for a temporary intravenous pacemaker lead remains a question of debate. Although prophylactic placement of a temporary pacemaker during ART for massive PE is not well established, the occurrence of severe bradyarrhythmias has been reported on multiple occasions (6). According to our ART protocol, pacemaker insertion was left to the operator's discretion; however, we subsequently mandated it because of the occurrence of prolonged third-degree atrioventricular block or asystole requiring temporary mechanical resuscitation in the first enrolled patients. In our experience, virtually all patients became temporarily pacemaker dependent, and this occurred a few seconds after the device activation and persisted for another 30–60 seconds after the ART device was deactivated. Although several hypotheses have been advocated to explain this bradyarrhythmic phenomenon, the most plausible one, in our opinion, is the massive release of neurohormonal substances such as bradykinins and adenosine secondary to the hemolysis induced by the ART device (7).

Additional concerns also related to the hemolysis caused by ART are the occurrence of severe hyperkalemia and hemoglobinuria. Hyperkalemia may exacerbate the electrical instability, and hemoglobinuria may cause further deterioration of kidney function in these patients already at risk of kidney failure because of hemodynamic instability and contrast medium administered for the ART procedure with or without diagnostic computed tomography angiography (8). The placement of a temporary pacemaker wire and the aggressive control of potassium levels are crucial during the ART procedure in patients presenting with massive PE.

Despite the aforementioned preventive measures, the neurohormonal release observed immediately after ART activation may cause refractory hypotension leading to impaired consciousness, syncope, seizures, or cardiac arrest (9). All these events are particularly deleterious in the setting of massive PE because they mandate airway protection with endotracheal intubation, which may precipitate hypotension potentially resulting in a refractory cardiac arrest. The afterload and preload reduction caused by the drugs used to induce general anesthesia are poorly tolerated in these patients because the failing right ventricle is highly preload dependent. Filling of the right ventricle may be further impaired by positive end-expiratory pressure ventilation used when the patient is intubated. For all these reasons, ART in patients presenting with massive PE should be performed, whenever possible, under local anesthesia, in the presence of a full resuscitative team (ie, interventionists and anesthesiologists).



a. **b.**

Figure. **(a)** Left pulmonary embolism involving the main inferior lobar artery (white arrows) and all the segmental arteries (black arrows). **(b)** After ART showing a *nearly complete* resolution of the thrombus in the lobar (white arrows) and the segmental (black arrows) arteries. White arrowheads indicate pacemaker wire positioned in the right ventricular free wall.

The occurrence of neurohormonal systemic side effects after ART activation indirectly confirms that this device is very efficacious in the fragmentation of the thrombus material. The excellent efficacy of ART in the case of massive PE was also observed by the significant improvement of the Miller index in the series by Chechi et al (3) and by the angiographic observations made in our series (**Figure**). As opposed to other vascular territories (eg, coronary arteries or lower extremities) where a maximal thrombus fragmentation and aspiration should be attempted, in massive PE, endovascular therapy should be aimed at improving hemodynamic status and not at obtaining an optimal angiographic result.

Overall, the excellent thrombus aspiration capacity of ART seems to be counterbalanced by deleterious systemic hormonal side effects. In our experience and in other published series, periprocedural deaths despite a satisfactory final angiographic result have been observed (3). The fact that ART itself produces hypotension confounds the efficacy of thrombus aspiration on hemodynamics, potentially leading the operator to continue thrombus aspiration unnecessarily. This paradoxical effect may start a vicious cycle (fragmentation/aspiration → hypotension → further fragmentation/aspiration → further hypotension) potentially leading to refractory right ventricular failure and death. In our opinion, a less efficacious thrombus aspiration in the absence of systemic neurohormonal side effects, as obtained with other PMT devices, may be sufficient to improve the pulmonary perfusion and the patient's outcome.

All these concerns emphasize the urgent need of a prospective multicenter trial randomly assigning patients with massive PE to systemic intravenous thrombolysis or to a modern PMT to define better the role of endovascular therapy in this particular high-risk setting.

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Drs. Kuo and Hofmann respond:

We appreciate the commentary offered by Bonvini et al on our metaanalysis of catheter-directed therapy (CDT) for massive pulmonary embolism (PE). Regarding their interpretation of our study, we wish to clarify certain points and to complement their thoughtful discussion with our own. Bonvini et al inquire whether the high success rate with CDT revealed in our study may have resulted from including mostly younger, healthier patients and patients with less severe or submassive PE. Although it is possible that CDT was selectively performed in some patients with relatively few comorbidities, and although we could not exclude the possibility of selection bias within studies, the selection effects overall were minimized because we limited data abstraction to patients with life-threatening massive PE (ie, PE associated with hemodynamic shock) (1).

During our research, we noted from the literature that almost all patients referred for CDT were patients with massive (not submassive) PE, and we carefully excluded the few cases of submassive PE from our study (1). Over the years, because CDT has been regarded as an experimental treatment offered at select institutions, it has typically been reserved for PE patients in extremis when all conventional therapies have failed. Bonvini et al claim that our results are more favorable than described in the review article by Kucher (2). First, the results of our comprehensive systematic review and rigorous metaanalysis are by definition more valid than any review article that lacks evidence-based methods. Second, Kucher's review describes a very high clinical success rate among cases of modern CDT (89.2%, n = 240) (2) in concordance with our study results (86.5%, n = 594) (1). In our discussion, we acknowledge this and firmly conclude that the results from our metaanalysis support and extend the general conclusions of earlier review articles, which all describe a high clinical success rate for modern CDT (1).

We commend the efforts of Bonvini et al for initiating a prospective study on CDT for PE, but we question their choice of device in using AngioJet Rheolytic Thrombectomy (ART) (Possis Medical, Minneapolis, Minnesota), a decision based solely on animal studies and in vitro tests. It is no longer necessary to rely on animal studies alone because meaningful data have been accumulated in human subjects treated with ART. From our metaanalysis, the highest complication rates occurred in the 68 patients who underwent CDT with the ART device including 27 minor complications (40%) and 19 major complications (28%), with five procedure-related deaths (1). In our study, 76% (19 of 25) of all major complications recorded were directly attributed to ART despite the fact that ART was used in only a small percentage (11%) of the 594 patients we studied (1). Conversely, our data indicated that most modern CDT (89%) was performed worldwide with a high degree of safety and efficacy without using ART.

We found that ART was the only device associated with bradyarrhythmia, heart block, hemoglobinuria, renal insufficiency, major hemoptysis, and procedure-related death (1). Several additional deaths related to ART have been recorded in the U.S. Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) database (3). As a result, the FDA has issued their strongest admonition—a black-box warning on the AngioJet device label pertaining to its use in patients with acute PE (Angiojet Xpeedior product insert, Possis Medical, Minneapolis, Minnesota, 2008:1–8). Over the years, such complications specific to ART have fueled the misperception that all CDT is risky treatment (4), and this has tarnished the overall reputation of endovascular PE therapy requiring justification for its ongoing use to treat acute PE (5). Nevertheless, a few centers will continue to use ART, some with industry support, despite the dangers and even though there is no proven advantage in terms of the efficacy and economic cost of ART relative to less expensive methods such as rotating pigtail fragmentation. In optimizing treatment for acute PE, we encourage all physicians to heed the oath *primum non nocere*—"first, do no harm." For all of these reasons, we believe the ART device should not be used as the initial mechanical option in future CDT protocols for treatment of acute PE.

Bonvini et al idealistically call for a randomized trial comparing catheter intervention with intravenous thrombolysis for acute massive PE. In reality, such a study would be unfeasible and unethical to perform. If we consider the study protocol for the current National Institutes of Health–funded ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) trial—a randomized study comparing baseline therapeutic anticoagulation versus the addition of catheter-directed thrombolytic therapy in patients with acute symptomatic deep vein thrombosis (DVT)—we notice immediately among the study's exclusion criteria that patients with the most severe form of DVT resulting in circulatory compromise and limb-threatening phlegmasia must be excluded from the study (6). According to the study's national principal investigator Dr. Suresh Vedantham, the reason such patients are excluded from the trial is that it would be unethical to randomly assign them to the control arm (personal communication, January 28, 2010). In other words,

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W.T.K. is a paid consultant and serves on the Scientific Advisory Board for Teneo Medical Development, Inc—Scientific Advisory Board. L.V.H. is on the Scientific Advisory Board for Bacchus Vascular and receives speaker honorarium from Portola Pharmaceuticals and Cook. None of our disclosures are related to the subject matter.

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