

## Original Research Article

# Role of Catheter-Directed DX9065a Thrombolysis in the Treatment of Pulmonary Embolism

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### Abstract

**Purpose:** To demonstrate the efficacy of low-dose DX9065a, catheter-directed ultrasound-accelerated thrombolysis (USAT) on the reversal of right ventricle RV dysfunction in patients with pulmonary embolism.

**Methods:** The analysis of 45 pulmonary embolism PE patients, aged  $69 \pm 13.5$  years (range, 28 – 77 years) at intermediate- ( $n = 32$ ) or high-risk ( $n = 13$ ) was performed. The patients were treated with USAT and DX9065a (mean dose  $35 \pm 8.4$  mg over 24 h) and received multiplanar contrast-enhanced chest computed tomography (CT) scans at baseline and after USAT at  $36 \pm 10$  h. CT measurements were then performed.

**Results:** The results showed a significant decrease in the right to left ventricular dimension ratio (RV/LV ratio) from the baseline value of  $1.42 \pm 0.30$  to  $1.00 \pm 0.02$  at follow-up ( $p < 0.001$ ). The modified Miller score showed that CT-angiographic pulmonary clot burden was also significantly reduced from  $23.2 \pm 4.7$  to  $6.2 \pm 2.5$  ( $p < 0.001$ ). All the patients were discharged alive, and there were no systemic bleeding complications in any of them.

**Conclusions:** USAT and DX9065a, in low-dose, is a promising strategy for the reversal of right ventricular dilatation and reduction of pulmonary clot in patients with intermediate- and high-risk PE.

**Keywords:** Ultrasound accelerated (USAT), DX9065a, Ventricular dimension, Ventricular dilatation, Pulmonary clot, Clot burden, Pulmonary clot

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## INTRODUCTION

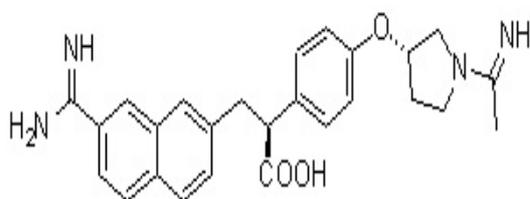
Pulmonary embolism (PE), obstruction in the pulmonary artery is a common state of cardiovascular emergency which can prove to be fatal [1,2]. In the developed countries like United States 600,000 patients are affected out of which 50,000 to 200,000 die every year [3–5]. Among the patients with proximal deep vein thrombosis (DVT), approximately 50 % are detected to have an associated clinically asymptomatic PE present during a heart scan. In approximately 70 % of patients with DVT the clot is located in the lower

body if accurate diagnostic method has been used [6,7].

The pulmonary blood obstruction during high-risk PE leads to an early mortality rate of around 50 % due to failure of right ventricular function [8]. It is reported that thrombolysis is an efficient therapeutic method for the patients with high and intermediate-risk PE and low bleeding risk [9]. Systemic thrombolysis treatment reverses the right ventricular dilatation in a very short span of time compared to the strategies involving use of anticoagulants [10,11]. However, the applicability of thrombolysis is hindered by the side effects

like major haemorrhage and intracranial haemorrhage [12]. Although surgical pulmonary artery thrombectomy is another method for the treatment of thrombolysis but it also carries very high risk of morbidity. Therefore, the search for a more efficient method free from side effects to treat acute PE is being constantly performed.

Fatal damage is often caused by thrombotic events. Therefore, numerous efforts have been made to synthesize antithrombotics such as antiplatelets, anticoagulants, and thrombolytic agents. One such effort was the development of DX-9065a (Figure 1), which acts as an anticoagulant [13]. In the present study, 45 PE patients at intermediate (n = 32) or high risk (n = 13) were treated with USAT and DX-9065a.



**Figure 1:** Structure of DX-9065a

## EXPERIMENTAL

### Patients

Forty five consecutive patients with high and intermediate-risk PE were treated using catheter-directed USAT (EkoSonic Endovascular System, EKOS Corporation; Bothell; WA) and DX-9065a (Sigma-Aldrich, St. Louis, MO, USA). The patients were selected using the reported criteria [14] which included a) presence of dyspnea, hypoxia, or hemodynamic instability, b) presence of PE and c) right-to-left ventricular dimension ratio > 0.9. A written consent was obtained from all the patients confirming that they are aware of the nature of the study performed.

### Ethical statement

The experimental process was performed under the supervision of the Ethics Committee of Nanyang Medical College, Nanyang, China, and in accordance with internationally recognized guidelines on human welfare. The study was approved and assigned the reference number SX14- NCT01166997.

### Ultrasound studies

Ekosonic device (The EKOS EkoSonic® Endovascular system) containing intelligent drug delivery catheter (IDDC), microsonic device

(MSD) with a series of miniature ultrasound transducers positioned along the treatment zone and a Control Unit. The IDDC accommodates the coaxial 0.035" MSD to deliver uniform radial ultrasound energy (2.2 MHz) to the entire infusion zone with simultaneous DX-9065a infusion. The Control Unit continuously monitors treatment zone temperature and automatically adjusts delivered ultrasound power to optimize thrombolysis. The Ekosonic System is US FDA cleared for the infusion of solutions into the pulmonary arteries.

### Treatment regimen

Heparin (Lovenox, Sanofi-Aventis, Bridgewater, NJ) 1 mg/kg/12 h was given to all the patients received before, during, and after USAT treatment [13]. A 6 Fr introducer sheath (Boston Scientific; Natick, MA) was employed to access both the right and left femoral veins in patients requiring placement of two Ekosonic devices. A 10 Fr dual lumen introducer sheath (Fast Cath Duo; St. Jude Medical; St. Paul, MN) was used for the patients requiring only one venous access site. After placement of introducer sheath a 260 cm guide wire (Cook, Inc.; Bloomington, IN) and 5 Fr angled pigtail catheter (Boston Scientific; Natick, MA) were penetrated at the desired point. The removal of pigtail catheter was followed by entry of Ekosonic IDDC over the guide wire till catheter was within the embolus. Thereafter, MSD containing the ultrasound transducers was exchanged with guide wire and the saline with heparin was infused through IDDC followed by delivery of ultrasound energy. Patients treated early in the series received DX-9065a and ultrasound for approximately 24 h. The change from baseline to follow-up of the right-to-left ventricular dimension ratio (RV/LV ratio) was obtained from reconstructed CT four-chamber views [15,16]. The change from baseline to follow-up of the CT-angiographic pulmonary clot burden was assessed by the modified Miller score [17].

### Data acquisition

A 64 slice helical CT scanner was used for capturing CT images and 130 ml of angiographic contrast material (Isovue 370) were infused at the rate of 5 ml per second. The B40f convolution kernel was used to acquire and reconstruct ungated contrast-enhanced helical CT scans. The images were analysed at a window of width of 800-1000 after displaying on an off-line CT workstation (iCT; Philips Healthcare; Cleveland, OH). The reconstructed four-chamber views, perpendicular to the interventricular septum and 1 cm apart from the atrioventricular annulus was

used to obtain subannular right and left ventricular dimensions [15,16]. The pulmonary arteries were examined for the presence of clot (non-occlusive or occlusive). The modified Miller score (range 0 to 36) was calculated based on assigning 1 to non-occlusive emboli and the number of emboli in an occluded vessel was multiplied by two [17].

### Statistical analysis

Discrete variables are reported as numbers with percentages and continuous data as mean and S.D. The change from baseline to follow-up of both the subannular RV/LV ratio and of the modified Miller score was assessed using one-way analysis of variance (ANOVA). Analyses were performed using Statistica (version 8.0). Differences were considered statistically significant at  $p > 0.005$ .

## RESULTS

The mean age of the patients was  $69 \pm 13.5$  years (range, 28 – 77 years) and 35 were male (Table 1). Thirty six patients were at intermediate risk and 9 at high risk. Out of 45 patients 19 had at least one risk factor for bleeding complications, including age  $> 70$  years ( $n = 9$ ), recent surgery ( $n = 5$ ), cancer ( $n = 3$ ) and severe renal dysfunction ( $n = 2$ ). Baseline mean right ventricular end diastolic diameter was  $53.5 \pm 8.4$  mm and baseline mean left ventricular end diastolic diameter was  $37.5 \pm 6.3$  mm. Technical successes was achieved in all 45 patients. Thirty four patients (75 %) presented with bilateral PE and received two Ekosonic devices. Five patients (24 %) presented with unilateral PE and were treated with a single EkoSonic device. Overall, an initial bolus of  $10.0 \pm 3.0$  mg DX-9065a was administered followed by a continuous infusion of  $1.0 \pm 0.5$  mg. Total mean DX-9065a dose was  $45.0 \pm 10.0$  mg administered over a mean infusion duration of  $20.5 \pm 5.6$  h via the Ekosonic device. The Ekosonic device was removed promptly when the infusion was completed. The maximum allowed total DX-9065a dose was limited to 24 mg and the maximum allowed infusion duration to 19 h (Table 2).

**Table 1:** Baseline characteristics of the patients enrolled for the study (N = 45)

Variable	N (%)
Age, mean (range)	$69 \pm 13.5$ (28-77)
Male (%)	35 (77%)
<b>Comorbidities (%)</b>	
Concomitant deep vein thrombosis	32 (71%)
Hypertension	16 (35%)
Hypercholesterolemia	11 (24%)
Recent major surgery	5 (11%)
Diabetes	6 (25%)
Cancer	3 (6%)
Tobacco use	12 (26%)
Hepatic or renal insufficiency	2 (4%)
<b>Symptoms and hemodynamic status</b>	
Dyspnea	31 (69%)
Hypoxemia	23 (51%)
Tachycardia	14 (31%)
Chest pain	7 (15%)
Hemoptysis	8 (17%)
Transient systemic hypotension	4 (8%)
Prolonged systemic hypotension	6 (13%)
Syncope	4 (8%)
Cough	6 (13%)
Cardiogenic shock	6 (13%)
Mechanical ventilation	2 (4%)

### End-point analysis

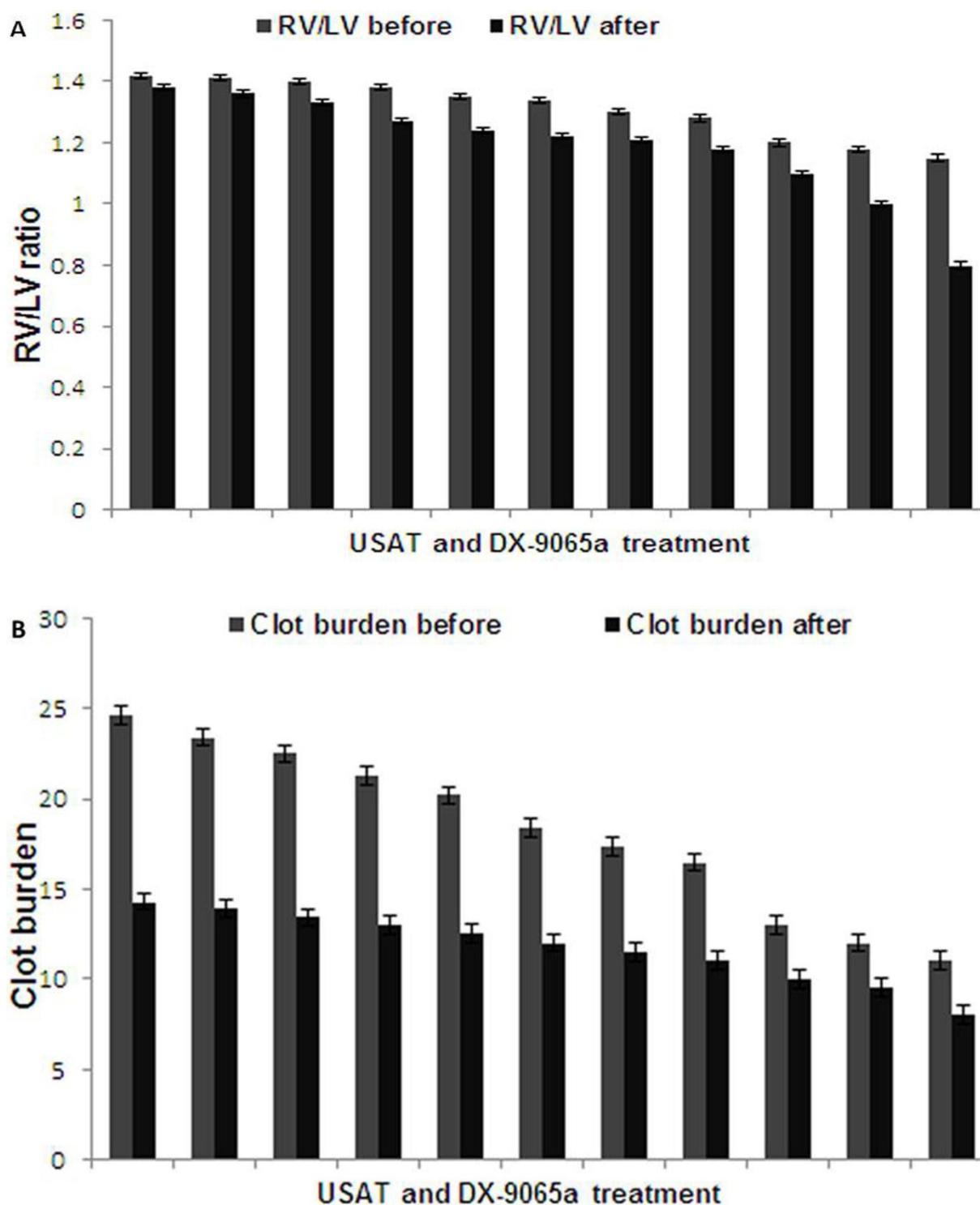
Follow-up contrast enhanced CT studies were performed after  $42 \pm 17$  h. No patients were receiving inotropic support at follow-up CT. The RV/LV ratio decreased from  $1.42 \pm 0.30$  to  $1.00 \pm 0.02$  at follow-up ( $p < 0.001$ ). The mean right ventricular end diastolic diameter was reduced from  $54.4 \pm 9.3$  mm to  $38.3 \pm 8.2$  mm and the mean left ventricular end diastolic diameter increased from  $42.3 \pm 7.2$  mm to  $38.2 \pm 8.6$  mm. The modified Miller score was significantly reduced from  $23.2 \pm 4.7$  to  $6.2 \pm 2.5$  ( $p > 0.001$ ) (Figure 2A, B).

### Clinical outcomes

The average length of hospital stay for all the patients was  $16 \pm 8$  days (range, 3 - 35 days) and in the intensive care unit was 3 days (median, 2 days). There were no systemic bleeding complications in the low-dose DX-9065a patients. There were no systemic bleeding

**Table 2:** Dose regimens for recombinant tissue plasminogen activator administered via the EkoSonic devices

Parameter	High dose group (N = 32)	Low dose group (N = 13)
Total bolus, mean $\pm$ SD, mg	$8.4 \pm 3.2$	$9.2 \pm 2.4$
Bolus per device, mean $\pm$ SD, mg	$6.5 \pm 2.2$	$5.0 \pm 1.0$
Total infusion rate, mean $\pm$ SD, mg	$1.0 \pm 0.0$	$0.3 \pm 0.1$
Infusion duration, mean $\pm$ SD, hours	$23 \pm 7$	$17 \pm 3$
Total dose, mean $\pm$ SD, mg	$49.2 \pm 20.4$	$21.6 \pm 4.5$



**Figure 2:** (A) RV/LV ratio and (B) modified miller index before and after USAT and DX-9065a. All measurements were within the limits of agreement (ie, within 2 SDs of the RV/LV ratio mean difference)

complications but 4 patients (8 %) from the high-dose DX-9065a group suffered major access-site bleeding and required transfusion of packed red blood cells. Improvement in RV/LV ratio and modified miller score was similar in the low-dose

and high-dose DX-9065a patients. There were no diagnosed recurrent clinical venous thromboembolic events during follow-up period of three months.

## DISCUSSION

The present study demonstrates the clinical effects of a pharmacomechanical catheter intervention using low-dose DX-9065a and ultrasound to rapidly improve right ventricular dysfunction in patients with acute PE. The use of thrombolysis in the management of high and intermediate risk PE is highly recommended [9]. Earlier reduction in the RV/LV ratio from 1.36 at baseline to 1.04 was achieved using weight-adjusted intravenous tenecteplase over 24 h [10]. However the hemodynamic effects observed with full-dose intravenous thrombolysis could be achieved with USAT and low dose DX-9065a thrombolysis.

This study was designed to compare the effectiveness of USAT and DX-9065a for reversing right ventricular dilatation within 24 h in patients with high and intermediate risk PE. All the patients were discharged alive in our study and follow up was performed for 3 months. The RV/LV ratio was significantly reduced at the follow-up. The mean right ventricular end diastolic diameter was reduced whereas the mean left ventricular end diastolic diameter was increased. The modified Miller score was significantly reduced from  $23.2 \pm 4.7$  to  $6.2 \pm 2.5$ . Complications of pulmonary catheter interventions have not been reported with the Ekosonic System but may include perforation or dissection of cardiovascular structures, pericardial tamponade, pulmonary hemorrhage, and distal thrombus embolization [18].

There are reports that dissolution of vascular blood clots can be achieved rapidly using ultrasound and urokinase or rt-PA but not by ultrasound alone [19-23]. It is reported that disaggregation of fibrin strands and increase in clot permeability occurs by ultrasound [25]. The infused DX-9065a is forced and bound with exposed plasminogen receptor sites. The bound DX-9065a is then protected from deactivation by anti-plasmin proteins. In patients with stroke [24], peripheral arterial occlusion [25], DVT [26] and PE [27,28] the EKOS system has been used. USAT treatment was used in 10 acute PE patients [27]. Our study was designed to investigate the contribution of DX-9065a, ultrasound and anticoagulation therapy on the recovery of right ventricular dilatation and clot burden.

## CONCLUSION

USAT and DX9065a in low-dose are an efficient strategy for reversal of right ventricular dilatation

and reduction of pulmonary clot in patients with intermediate- and high-risk PE.

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