

# Intravenous thrombolysis associated with a high risk of hemorrhagic transformation in ischemic stroke patients with cardiac myxoma and over 70 years of age

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## Abstract

**Objectives:** Although thrombolytic therapy has been shown to be beneficial to stroke patients, its safety and effectiveness in stroke patients with cardiac tumor is unknown. This study assessed the safety and efficacy of intravenous thrombolysis with recombinant-tissue plasminogen activator (rt-Pa) in stroke patients with cardiac myxoma. **Methods:** We systematically searched databases for all publications on thrombolysis in patients with cardiac tumor-related strokes. The literature on thrombolysis in ischemic stroke patients with myxoma was systematically analyzed; information on the hemorrhagic transformation and response rates in patients over and under 70 years of age was extracted and compared. Statistical tests were performed to evaluate the odds ratios for these factors. **Results:** Twelve case reports were identified. Four patients were 70 years of age or older, two (50%) of whom had demonstrated hemorrhagic transformation, which was not found in patients under 60 years of age. The rate of response to treatment was 60% (3/5) in patients under 60 and 25% (1/4) in those  $\geq 70$  years of age. The rate of hemorrhagic transformation in the patients  $\geq 70$  years of age was higher than that in patients  $< 70$  years of age (odds ratio 7).

**Conclusion:** Intravenous thrombolysis in ischemic stroke patients with myxoma who were over 70 years of age was associated with a lower response rate and a higher risk of hemorrhagic transformation.

## INTRODUCTION

Myxoma, which is the most common primary cardiac tumor, can cause embolic cerebral infarction or intracranial hemorrhage.<sup>1</sup> Intravenous (IV) recombinant-tissue plasminogen activator (rt-PA), which is now administered to ischemic stroke patients within 3 hours of stroke onset, has been found to improve patient outcome.<sup>2</sup> However, a previous study reported that thrombolysis in a patient with cardiac thrombus caused embolic stroke.<sup>3</sup>

The increased use of thrombolytic therapy has also seen increased reports of thrombolysis in stroke patients with cardiac myxoma in the recent years. As the safety and efficacy of thrombolysis in stroke with cardiac myxoma is still unclear, we undertake to review the literature on IV thrombolytic therapy in ischemic stroke patients with cardiac myxoma to evaluate the risk of hemorrhagic transformation and their outcome of treatment. We hope this review will help clinicians to decide whether to administer IV thrombolytic

therapy to stroke patients with cardiac tumors.

## METHODS

We systematically searched PubMed, proQuest, the Directory of Open Access Journals and Embase databases up to January 2012 for all publications on thrombolysis in patients with cardiac tumor-related strokes. The search terms used were the following: thrombolysis and/or thrombolytic therapy, or recombinant-tissue plasminogen activator and myxoma. Because no publications on clinical trials in stroke patients with myxoma were available, we included case reports of thrombolysis in stroke patients with myxoma and any report that investigated thrombolytic therapy in patients with cardiac tumor-related strokes. All of the publications were written in English or in Japanese with an abstract in English. We ensured that the diagnosis of cardiac myxoma was confirmed by the following appropriate imaging tests: transthoracic sonography or computed tomography (CT). A “good response” was defined

as improvements in symptoms or a reduction of 4 points or more on the National Institutes of Health stroke scale (NIHSS) within the first 7 days after thrombolytic therapy. "No response" was defined as reductions of less than 4 NIHSS points or no reported improvements in symptoms within the first 7 days after thrombolytic therapy. The statistical software used was Graphpad Prism 5 (Graphpad software, Inc. La Jolla, Ca, USA).

## RESULTS

The systematic search found 12 case reports of IV thrombolysis in ischemic stroke patients with cardiac tumors. One patient had a fibroelastoma, one had bilateral atrial myxoma, eight patients had left atrial myxoma and two had left ventricle myxoma (Table 1). The patients were aged 22-79 years; three patients (25%) were under 45 years of age. Three of the 12 (25%) patients were women. One 74-year-old woman had symptoms of global aphasia with normal muscle strength and sensation. A CT of her brain showed a left frontal infarct. She experienced vomiting and weakness in her right hand and a repeated brain CT showed a right cerebellar hemorrhage and a small left parietal subarachnoid hemorrhage 5 hours after thrombolytic therapy.<sup>12</sup> However, her symptoms improved during the 1-week course of treatment with intact repetition but dysfluency and impairment of comprehension continued, which was compatible with the magnetic resonance imaging (MRI) finding of a left frontal infarct. One 63-year-old woman had a right middle cerebral artery infarct and left hemiparesis. After thrombolytic therapy, her symptoms did not improve. A CT of her brain conducted 24 hours after thrombolytic therapy did not show a hemorrhage, whereas an asymptomatic hemorrhagic transformation was revealed in a CT image taken after 25 days.<sup>11</sup> This hemorrhagic transformation may have been due to the large infarction and not related to the thrombolytic therapy. One 79-year-old man had a left middle cerebral artery occlusion. He had undergone thrombolytic therapy within 3 hours of stroke onset. On the second day, brain CT showed a hemorrhagic transformation in the area of the left middle cerebral artery.<sup>13</sup> Nine patients experienced no hemorrhagic transformation. Of the 12 patients, three were aged between 60 and 69 years, and four were aged 70 years or over. Two (50%) patients  $\geq 70$  years of age experienced hemorrhagic transformation after thrombolytic therapy, whereas no hemorrhage was found in the patients less than 60 years of age (Figure 1). The

hemorrhagic transformation rate in the patients who are  $\geq 70$  years of age was higher than that in those under 70 years of age (odds ratio, 7). Three of the five (60%) patients who were aged between 20 and 59 years, two of the three (66.7%) patients who were aged between 60 and 69 years, and one of the 4 (25%) patients aged  $\geq 70$  years showed a good response to thrombolytic therapy. (Figure 2). The response rate was lower in the patients aged  $\geq 70$  than those in patients under 70 years of age (odds ratio 0.2).

## DISCUSSION

The safety and effectiveness of thrombolytic therapy in ischemic stroke patients with myxoma can only be evaluated by an adequate randomized and controlled trial. However, because primary cardiac tumors are rare, with a prevalence of about 7 per 10,000,<sup>9</sup> such a trial is not feasible.

In the absence of a randomized controlled trial, a review of all of the prior case reports and an analysis of their results were considered to be an appropriate research design. Because the beneficial effect of IV thrombolysis in stroke patients has been well established,<sup>2</sup> the use of IV thrombolysis in stroke patients with myxoma in recent years has also increased.

Generally, strokes mostly occur in patients over 55 years of age. In a large population-based study, only 10.83% of all strokes occurred in individuals aged  $< 55$  years.<sup>16</sup> In the present review, five (41.6%) of the 12 patients with cardiac myxoma and stroke were under 55 years of age, and four (33.3%) were young ( $\leq 45$  years).<sup>17</sup> The results suggest that cardiac myxoma is a risk factor for young stroke.

Of the 12 patients in this review, three patients (25%) developed hemorrhage after thrombolytic therapy. According to Bhatnagar *et al*, the hemorrhagic transformation rate in patients who received IV rt-Pa therapy ranged from 2% to 13.6%.<sup>18</sup> In this report, 33.3% (1/3) of patients aged between 60 and 69 years and 50% (2/4) of patients aged  $\geq 70$  years experienced hemorrhagic transformation, showing that IV rt-Pa in ischemic stroke patients with myxoma who are  $\geq 70$  years of age may increase the risk of hemorrhagic transformation. Four of the 12 patients did not undergo hemorrhagic transformation and did not respond to thrombolytic therapy. The response rate was lower in patients who are  $\geq 70$  years of age. The lack of response to thrombolytic therapy may be due to tumor emboli from the myxoma, which can not be lysed by IV rt-Pa.

No patient under 60 years of age developed

**Table1. Characteristics of published patients with stroke and cardiac myxoma**

No	Age	Sex	Myxoma	Stroke type	rt-Pa infusion	Outcome		Reference
						Hemorrhage	Response	
1	51	M	Bilateral atrial (L: 4.7x2.7 cm) (R: 2.6x1.1 cm)	CT: no abnormal finding (left middle cerebral artery territory)	Yes (84 minutes)*	No	Good	4
2	41	M	Cardiac papillary fibroelastoma (1.5x0.9 cm)	CT: Right middle cerebral artery territory	Yes (105 minutes)*	No	Good	5
3	70	M	Left atrium (7.0x 2.5x 1.5 cm)	MRI: Left middle cerebral artery	Yes (92 minutes)* 0.6mg/Kg	No	Good	6
4	26	M	Left atrium (6.4x 5x 4 cm)	MRI: Right middle cerebral artery territory	Yes (65 minutes)* 90 mg	No	Good	7
5	45	M	Left atrium (8x4.7x 3.7 cm)	CT: left putamen and caudate nucleus	Yes (172 minutes)* 0.9mg/Kg	No	No	8
6	64	M	Left ventricle (2.0x 2.5 cm)	CT: left hemisphere	Yes	No	Good	9
7	22	F	Left ventricle (3.0x 4.0 cm)	MRI: Right middle cerebral artery territory	Yes (185 minutes)* 0.9mg/Kg	No	No	10
8	63	F	Left atrium	CT: right middle cerebral artery infarct	Yes	Yes	No	11
9	74	F	Left atrium	MRI: left frontal lobe infarct	Yes (180 minutes)*	Yes	No	12
10	79	M	Left atrium (2.1x1.2 cm)	Left middle cerebral artery infarct	Yes (180 minutes)*	Yes	No	13
11	72	M	Left atrium (6.7x2 cm)	CT, MRI: right middle cerebral artery territory infarct	Yes (100 minutes)* 0.6mg/Kg	No	No	14
12	65	M	Left atrium (3.6x5.6 cm)	CT: left middle cerebral artery territory infarct	0.7mg/Kg	No	Good	15

Rt-Pa: recombinant-tissue plasminogen activator; CT: computed tomography; MRI: magnetic resonance imaging.

\*Minutes from symptom onset to thrombolytic therapy

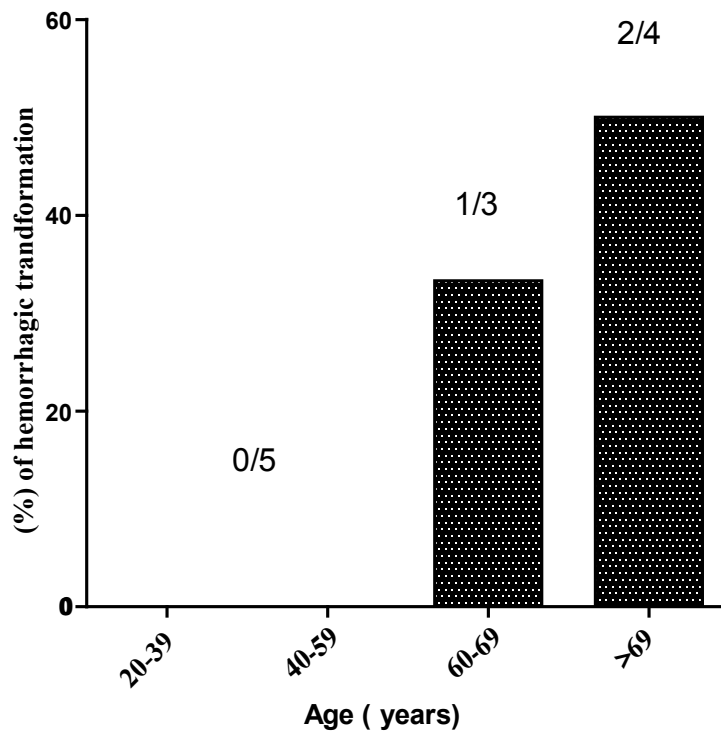


Fig 1. Hemorrhagic transformation in stroke patients with cardiac myxoma and thrombolytic therapy

a post-thrombolytic hemorrhage. It has been reported that myxomatous material in cerebral vessels may induce vessel wall inflammation and leading to vessel wall weakening and aneurysm dilatation.<sup>12</sup> Whether the higher risk of hemorrhage in older patients is related to vessel wall weakness and/or aneurysmal dilatation needs further investigation.

The limitations of the study were the following: 1). the patient information in this meta-analysis was from single case reports rather than trials; and 2). unpublished cases could not be included; although every effort was made to include all published literature.

In conclusion, our analyses suggest that it is safe to administer IV rt-Pa to acute ischemic

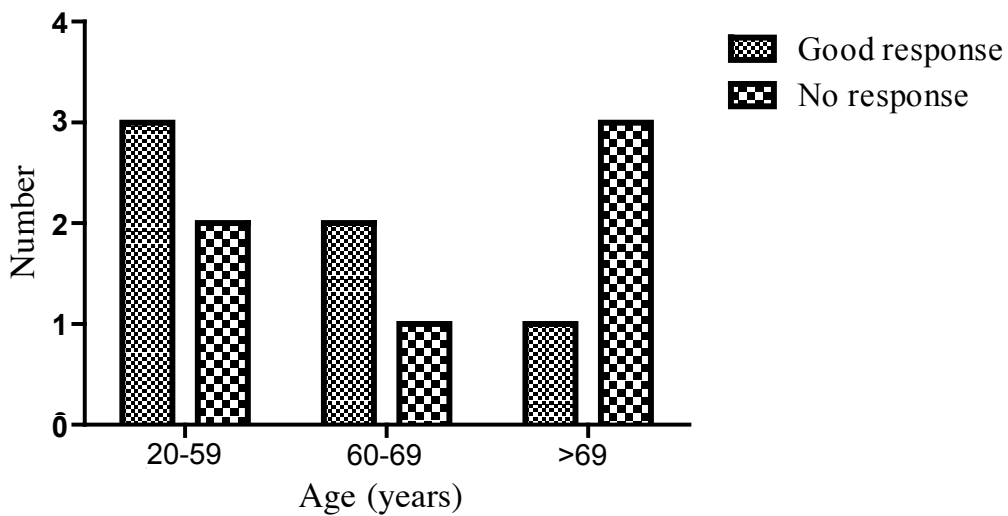


Fig 2. Stroke patient with cardiac myxoma response to thrombolytic therapy

stroke patients with myxoma who are under 60 years of age. However, in stroke patients with cardiac myxoma who are  $\geq 70$  years of age, IV rt-Pa is associated with a lower response rate and a higher risk of hemorrhagic transformation.

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