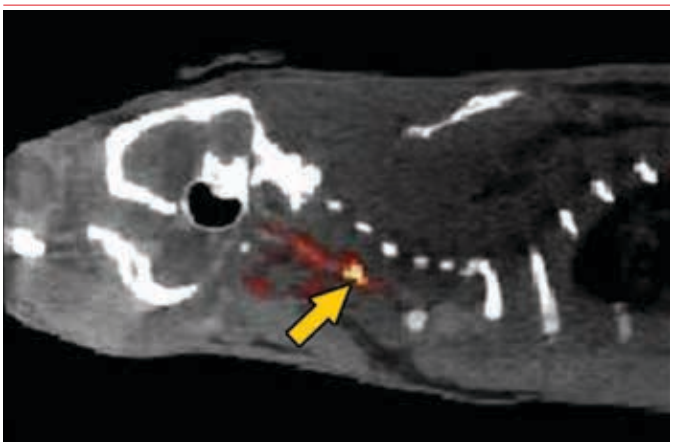
observations following treatment with recombinant tissue plasminogen activator (rt-PA) to quantitatively assess clot bursting. Following sacrifice, *ex-vivo* assessments of thrombolysis, and probe biodistribution were also performed.

Imaging revealed the specificity of FBP7 for the thrombus (Figure 1). Binding to the thrombus exceeded binding in the left carotid, brain, and heart by ~4-, 12-, and 2.5-fold, respectively, soon after the injection of FBP7. The binding specificity to the thrombus was maintained with time (90 minutes), while binding to the other regions diminished. Examination at 4 hours post injection revealed the same uptake of FBP7 to the thrombus, but reduced binding in the other regions, resulting in lower background; thrombus binding of the probe exceeded binding to the left carotid, brain, and heart by ~15-, 65-, and 10-fold, respectively.

Figure 1. FBP7 Detects Mural Thrombosis at the Level of the Common Carotid Artery (arrow). Fused PET-CT image.



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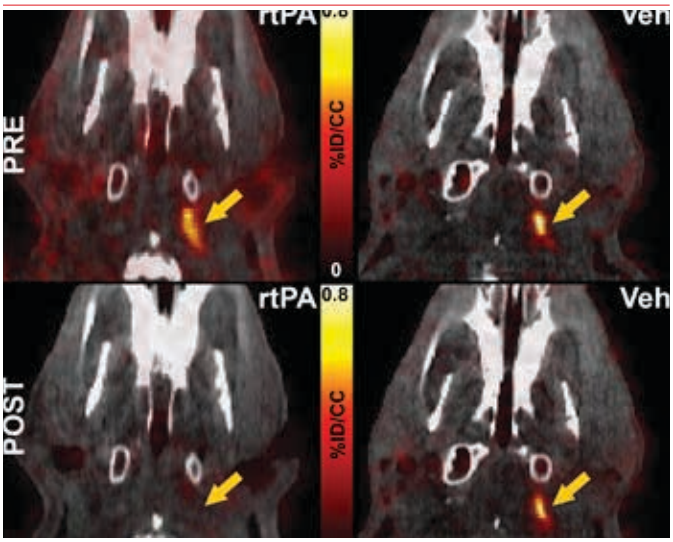
PET-CT imaging in the embolic stroke model revealed the specificity of FBP7 for the detection of the embolus at the level of the internal carotid artery and the middle cerebral artery, common sites of occlusion in human strokes. Furthermore, the dissolution of the embolus following administration of rt-PA was evident, while probe binding remained constant in rats who received vehicle instead of rt-PA (Figure 2).

Figure 2. FBP7 Detects Thrombolysis in the Internal Carotid Artery After Treatment With rt-PA, but Not Vehicle. Fused PET-CT images.



rt-PA=recombinant tissue plasminogen activator; Veh=vehicle.

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Table 2 summarizes the study conclusions.

Table 2. Study Conclusions

- PET imaging of thrombosis and thrombolysis is feasible using FBP7
- FBP7 imaging enables detection of nonocclusive (mural) and occlusive thrombi
- FBP7 can be used to visualize and quantify thrombolysis after rtPA administration

FBP7=fibrin-binding probe 7; PET=positron emission tomography; rt-PA=recombinant tissue plasminogen activator.

FBP7 is a very promising candidate for clinical testing. Dr. Blasi added that this proof-of-concept study is now being followed by assessments of the capability of the probe to quantify the level of fibrin in thrombi and to detect different stages of the thrombus evolution.

Dr. Blasi received the Mordecai Y. T. Globus New Investigator Award in Stroke at the International Stroke Conference 2014 for his work on molecular imaging of thrombosis.

Stroke Neuroprotection of Prehospital Magnesium Sulfate Explored

Written by **Brian Hoyle**

Magnesium sulfate administered to patients <2 hours after stroke fails to provide neuroprotection. The primary findings of the Field Administration of Stroke Therapy–Magnesium trial [FAST-MAG] were presented by Jeffrey L. Saver, MD, Stroke Center, University of California at Los Angeles, Los Angeles, California, USA.

Early intervention is critical for stroke care. Delayed time to treatment after onset of stroke symptoms can result in progressive neuron loss and diminished outcome [Lansberg MG et al. *Stroke* 2009; Saver JL. *Stroke* 2006; Saver JL et al. *Stroke* 2004]. The physiological and neuroprotective prowess of magnesium has been amply demonstrated in animal models of stroke. Prehospital administration of magnesium by emergency medical services (EMS) providers can accelerate treatment by nearly 2 hours [Saver JL et al. *JAMA* 2013; Saver JL et al. *Stroke* 2004]. Yet, patient benefits of this 'in-field' treatment are unclear.

The FAST-MAG trial was undertaken to explore whether paramedic administration of magnesium is effective and safe for treatment of acute stroke. The placebo-controlled, double-blind, randomized, Phase 3 trial from January 2005 through March 2013 involved 60 hospitals (952 physicians) and 40 EMS provider agencies (2988 paramedics) throughout Los Angeles and Orange Counties. The 1700 patients received 4 g magnesium sulfate (n=857) or placebo (n=843) within 2 hours of the onset of stroke symptoms. All patients received 16 g maintenance magnesium sulfate within 24 hours. Inclusion criteria were suspected stroke according to the Los Angeles Prehospital Stroke Screen, age 40 to 95 years, last known well time within 2 hours of treatment initiation, and deficit present for ≥15 minutes.

The primary endpoint was the mRS stroke disability score. Secondary endpoints were mRS 0-1 and 0-2, Barthel Index scores of daily living, NIHSS scores, and Stroke Impact Scale scores.

The study arms were comparable in a battery of baseline characteristics and neurological features. There was no difference in the time from onset of symptoms to administration of placebo or magnesium. This shows that the EMS system succeeded in giving drug early after stroke even if the treatment was not effective. The 3-month mRS scores were not significantly different for both arms (Table 1). None of the secondary endpoints differed appreciably between the study arms (Table 2).

Table 1. Global Disability at 3 Months Based on mRS Scores

mRS Scale	Patients (%)	
	Placebo n=843	Magnesium n=857
0	21.7	20.9
1	15.2	15.6
2	15.9	15.9
3	10.8	12.6
4	9.5	10.4
5	11.5	9.3
6	15.4	15.3

Table 2. Secondary Endpoint Data

Endpoint	Placebo n=843	Magnesium n=857	p Value
mRS 0-1	36.9%	36.5%	0.97
mRS 0-2	52.8%	52.4%	0.87
Barthel 95-100	51.6%	49.8%	0.46
Barthel 60-100	66.1%	69.2%	0.17
NIHSS	13.4±17.5	12.4±17.0	0.28
Stroke Impact Scale	65 (range, 5–92)	67 (range, 12–92)	0.32

Subgroup analyses failed to reveal benefits of magnesium depending on use/non-use of tissue plasminogen activator, treatment within 60 or 120 minutes, age, gender, race, and stroke severity. Serious adverse events occurred in 50.1% and 51.2% of patients in the placebo and treatment arm, respectively (p=0.66).

Possible explanations for the disappointing results include slow passage of magnesium across the blood-brain barrier and the inability of magnesium to prevent the ischemic cascade.

New Study Reveals That TCD Is Better Used to Detect PFO Than TEE

Written by **Masha Dowell**

About 25% of the world's population has been reported to have patent foramen ovale (PFO) or symptoms related to it, and they are at a greater risk of paradoxical embolisms [Kent DM, Thaler DE. *Stroke* 2010; Homma S, Sacco RL. *Circulation* 2005]. J. David Spence, MD, Robarts Research Institute of Western University, London, Ontario, Canada, presented new research that revealed that transcranial doppler (TCD) ultrasound is superior to transesophageal echocardiography (TEE) for the detection of PFOs associated with higher stroke risk.

Previous studies have focused on which PFO patients were most likely to have paradoxical embolisms. Clinical clues to paradoxical embolism have included pulmonic surges, dyspnea, tachycardia at onset, extended travel or sitting, previous deep vein thrombosis, and others. Small studies suggest that patients with paradoxical embolism had larger shunts, septal mobility [De Castro S et al. Stroke 2000], and atrial septal aneurysm [Mas J-L et al. *N Engl J Med* 2001]. More recent studies (the Northern Manhattan study and the ROPE study) have documented that neither septal aneurysm nor mobility predict strokes, however [Di Tullio MR et al. *J Am Coll Cardiol* 2013; Wesseler B et al. *Circ Cardiovasc Imaging* 2013].

In this trial, the research team studied the performance of TCD, in comparison with TEE, as it relates to the detection of high risk PFO. Of those patients (n=340) included in the research, 61.5% were women with a mean age of 53 years.