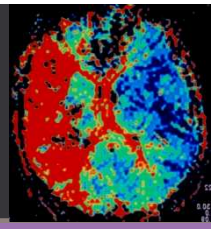
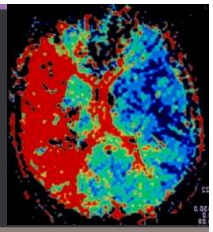
Neurovascular Unit-
Hospital Vall d´Hebron
Barcelona

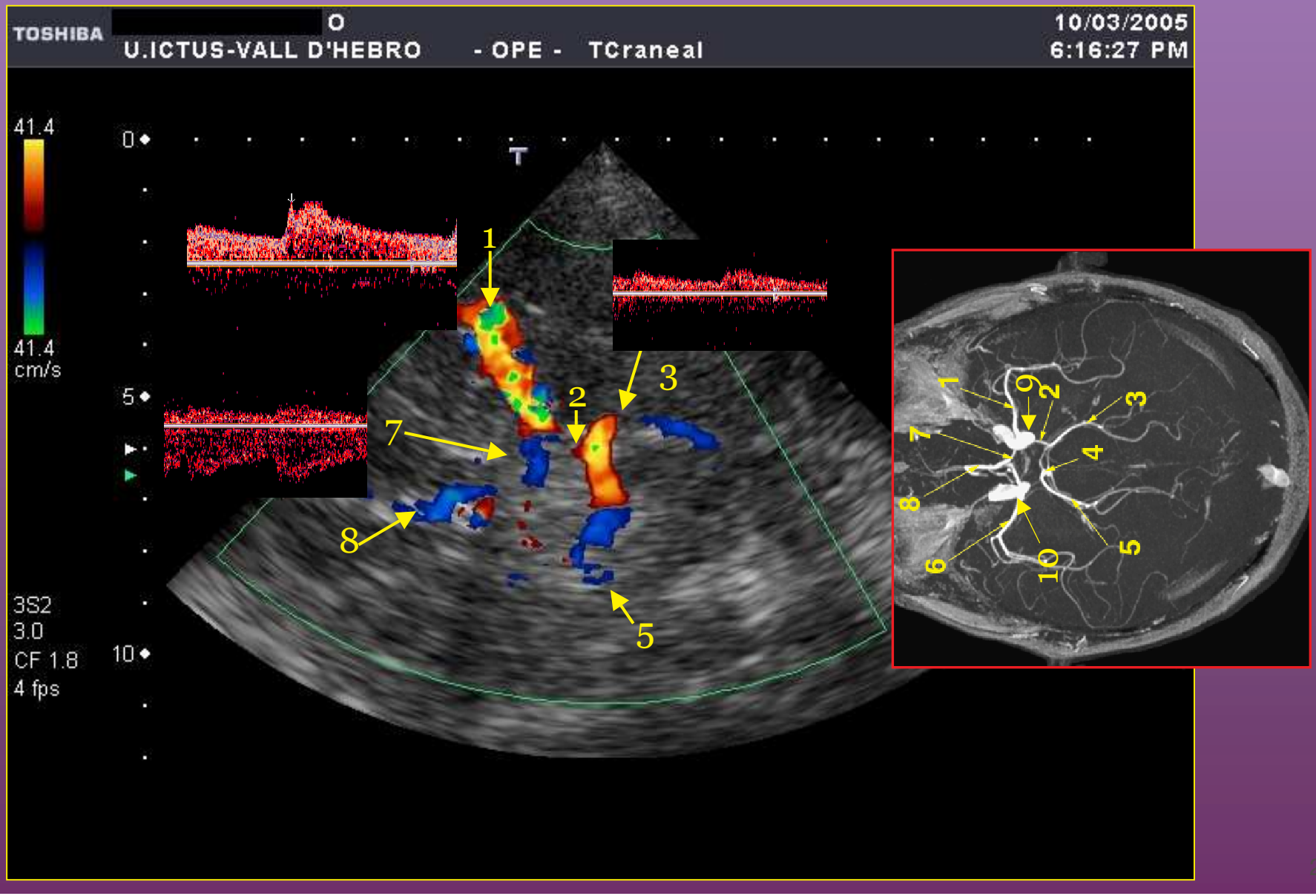


Sonothrombolysis for acute ischemic stroke

Lavinia Dinia
Carlos A. Molina

TCD in acute stroke





Advantages of TCD-TCCS in acute stroke

Location of arterial occlusion

Evaluation of collateral flow

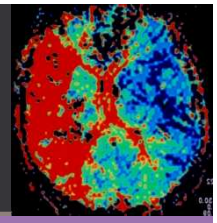
Recanalization monitoring

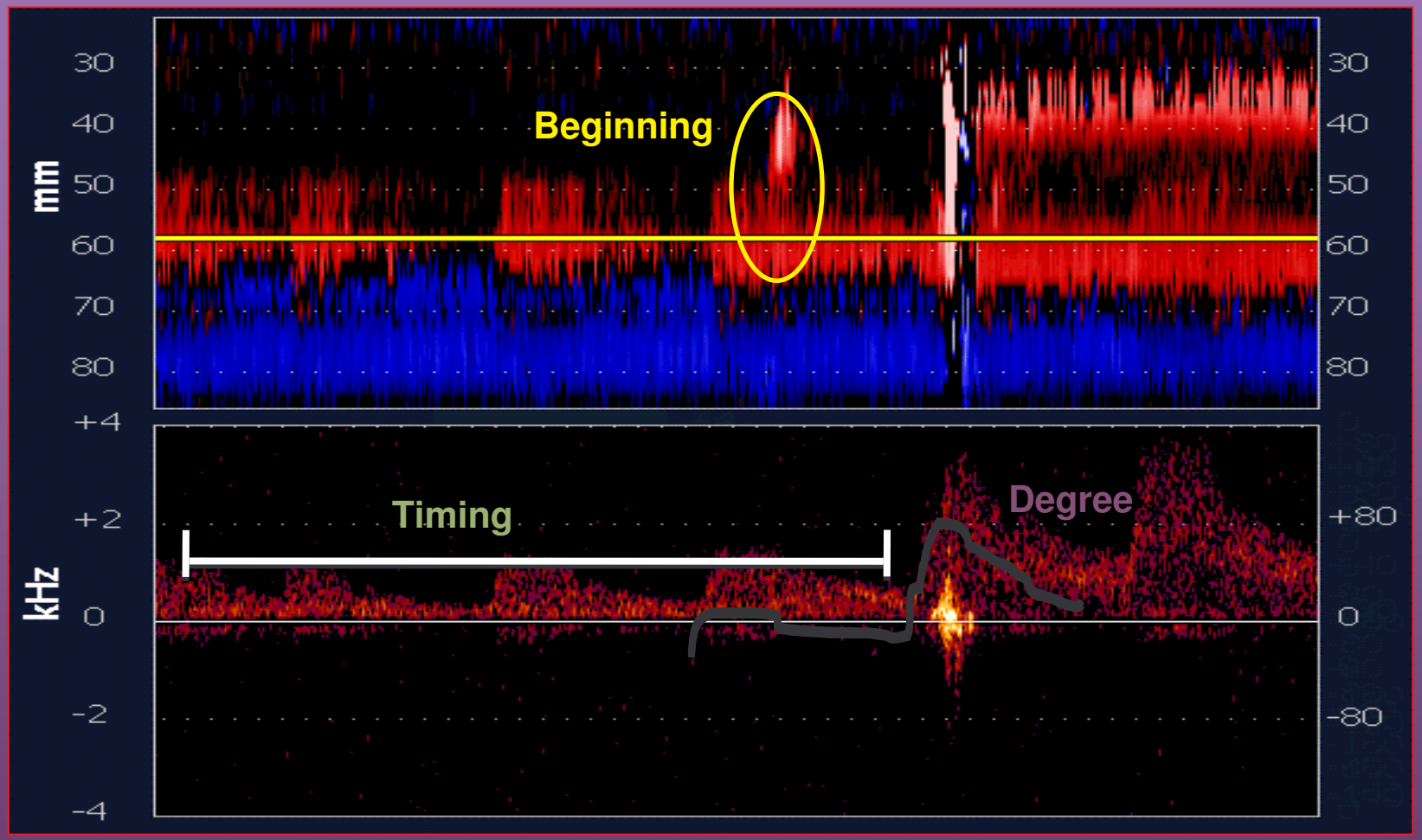
Re-occlusion

Enhance the fibrinolytic action of tPA

Recanalization monitoring

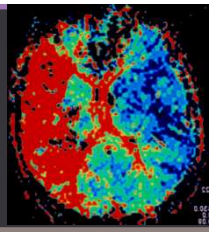
TCD continous monitoring

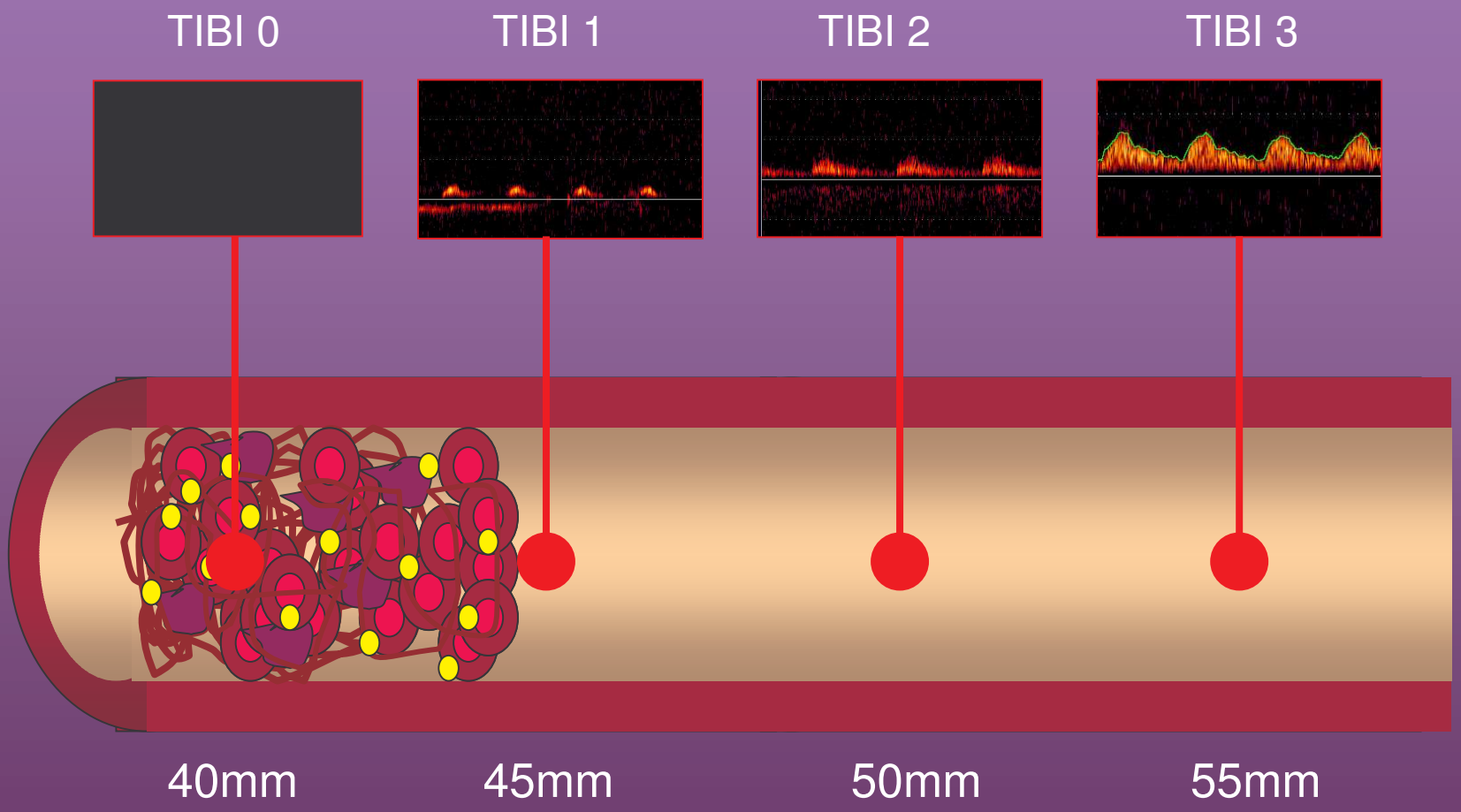




Correlation with clinical course and outcome

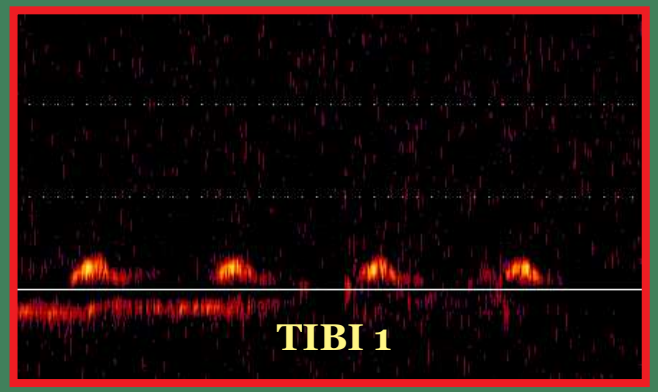
TIBI (Thrombolysis In Brain Ischemia) grading system

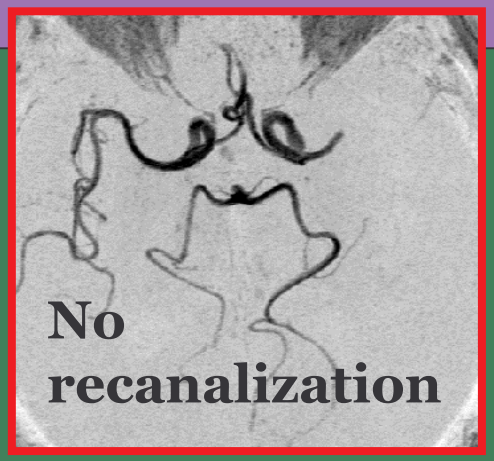


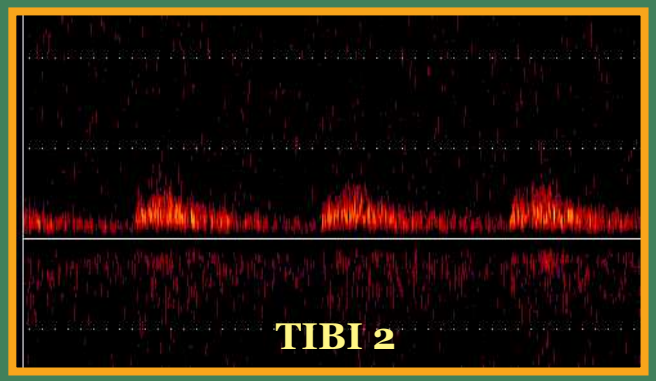


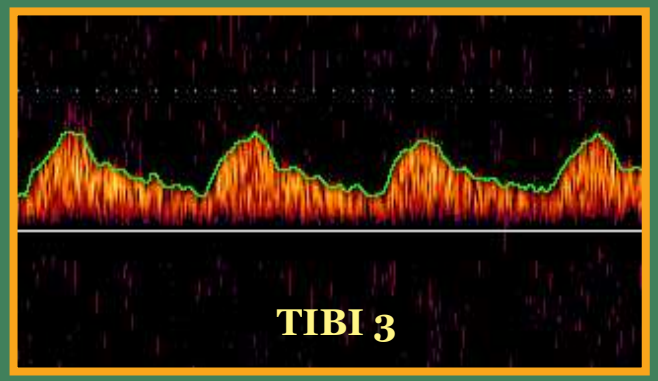
Demchuk AM et al. Stroke. 2001;32:89–93.

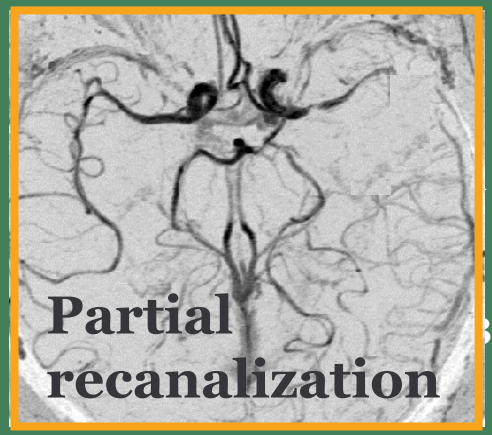
Determination of recanalization

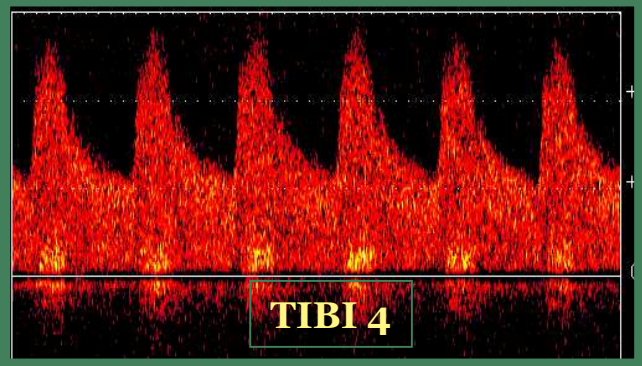


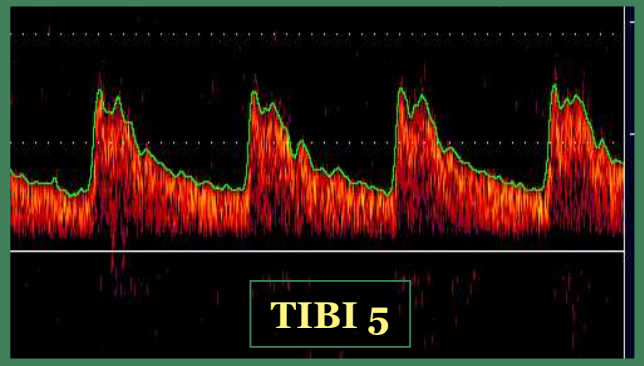


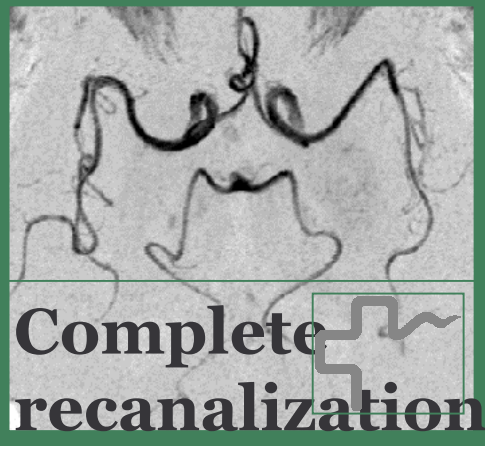




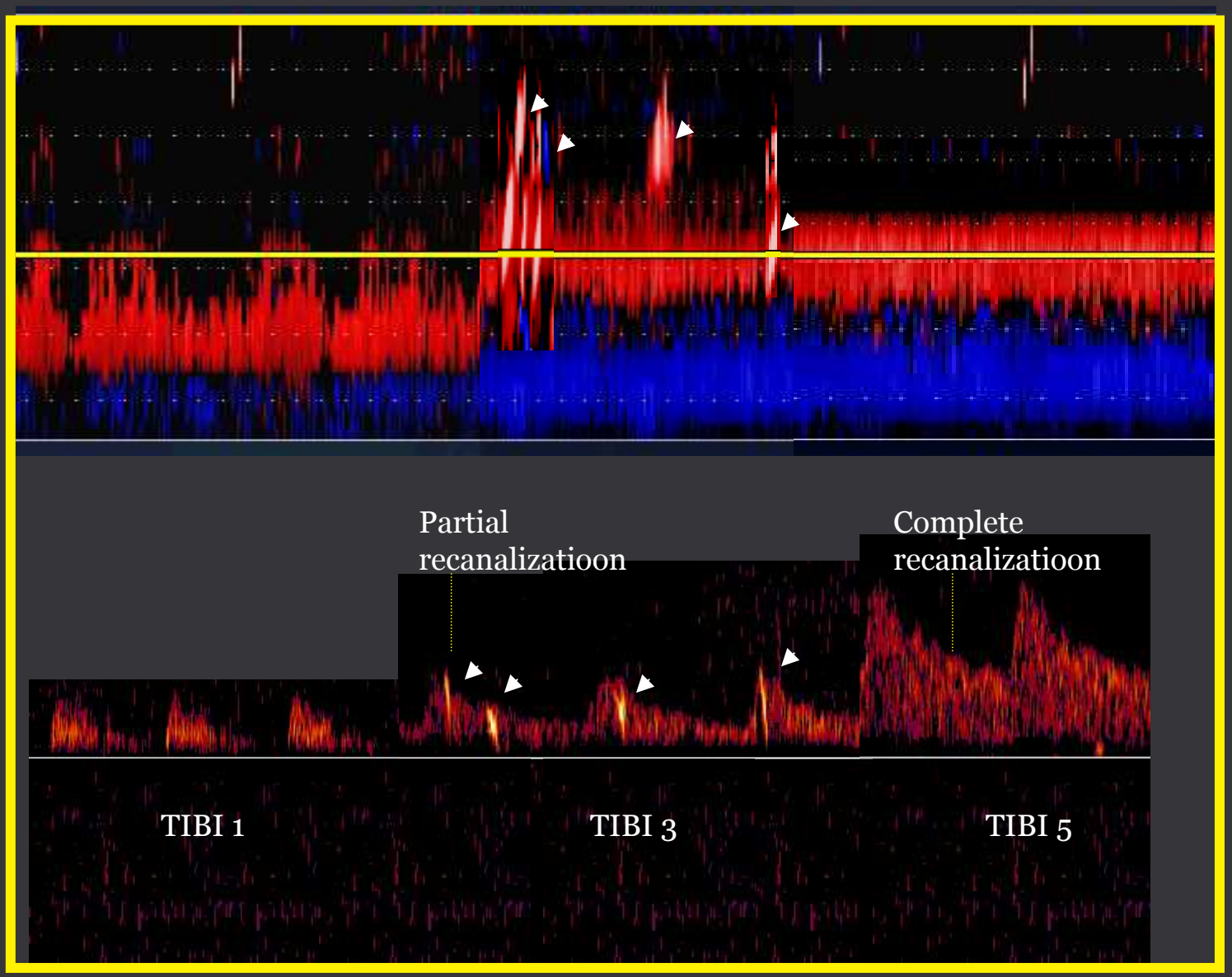






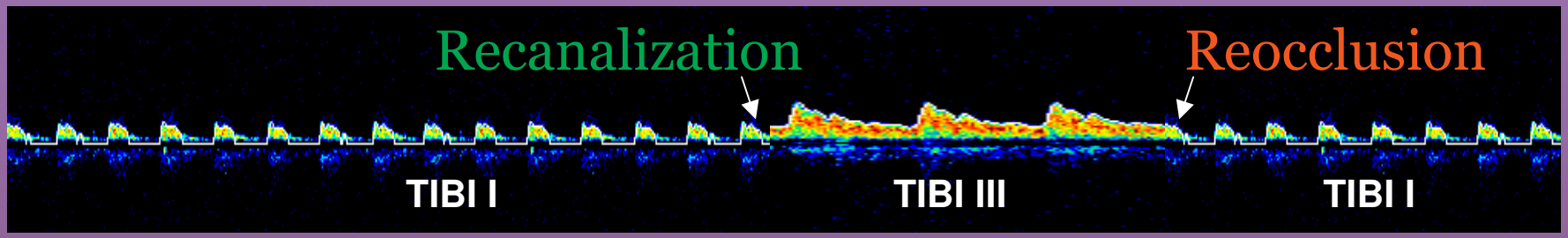


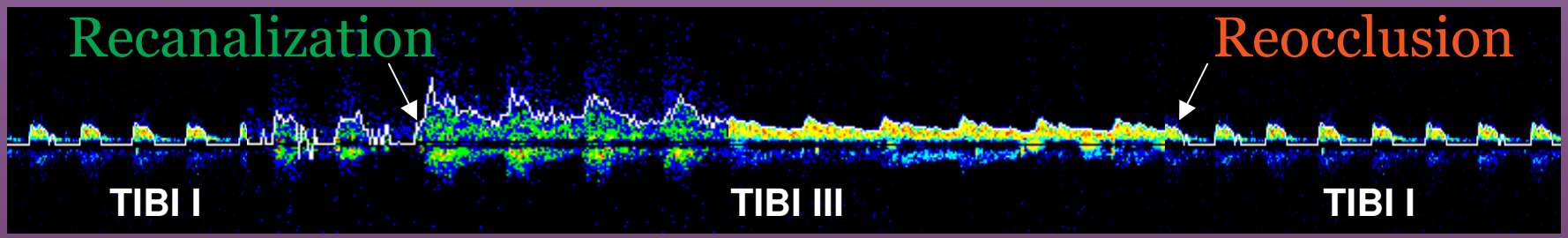
Dynamic of tPA-induced clot dissolution in acute stroke



Delgado-Mederos et al Eur J Neurol 2005

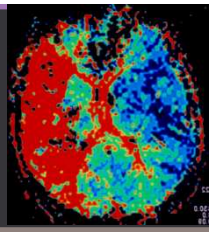
Re-occlusion





Reocclusion is usually defined as a worsening in 1 grade in the TIBI flow grading system after a previously documented recanalization.

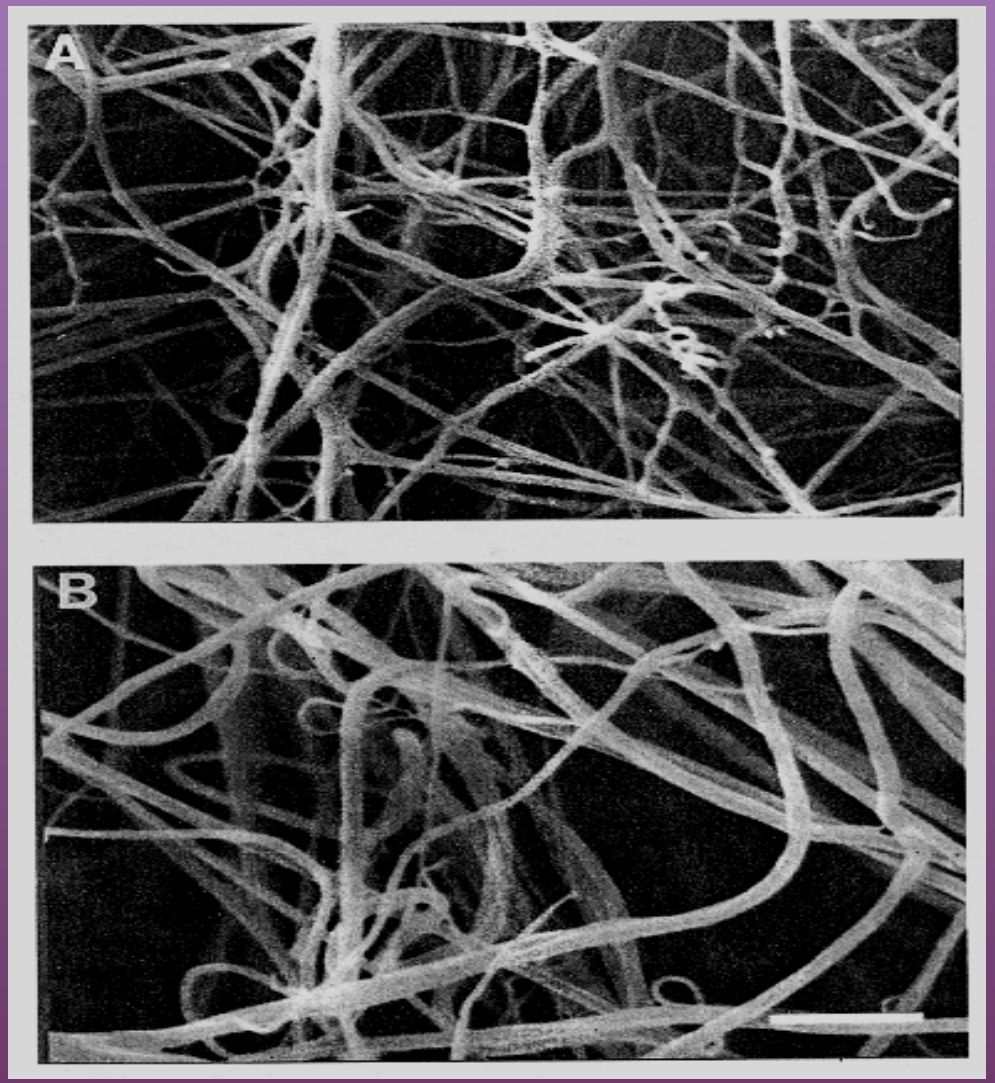
Sonothrombolysis
Reversible changes in fibrin mesh



Before

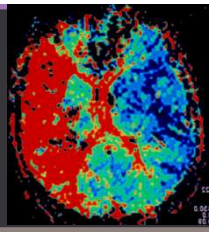
During

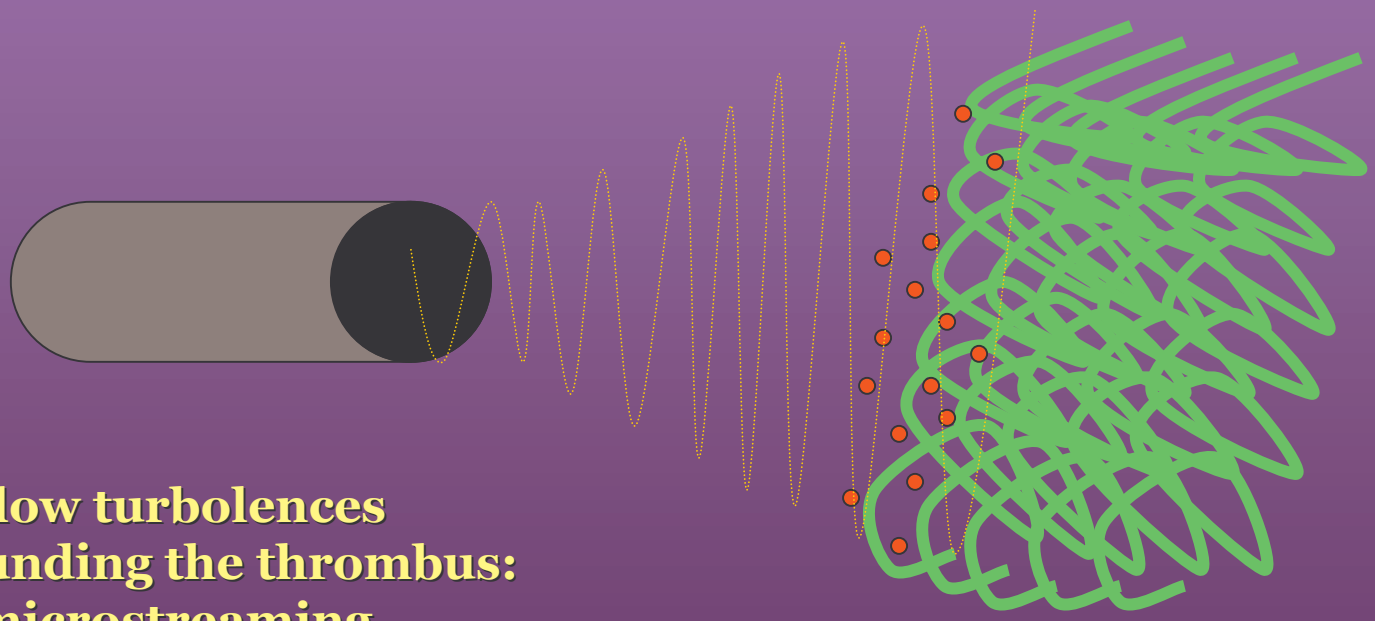
After



Braaten y coll .Thromb Haemost 1997

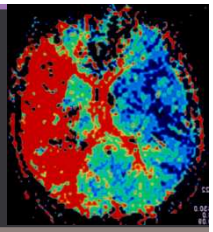
Sonothrombolysis
Better tPA penetration and distribution

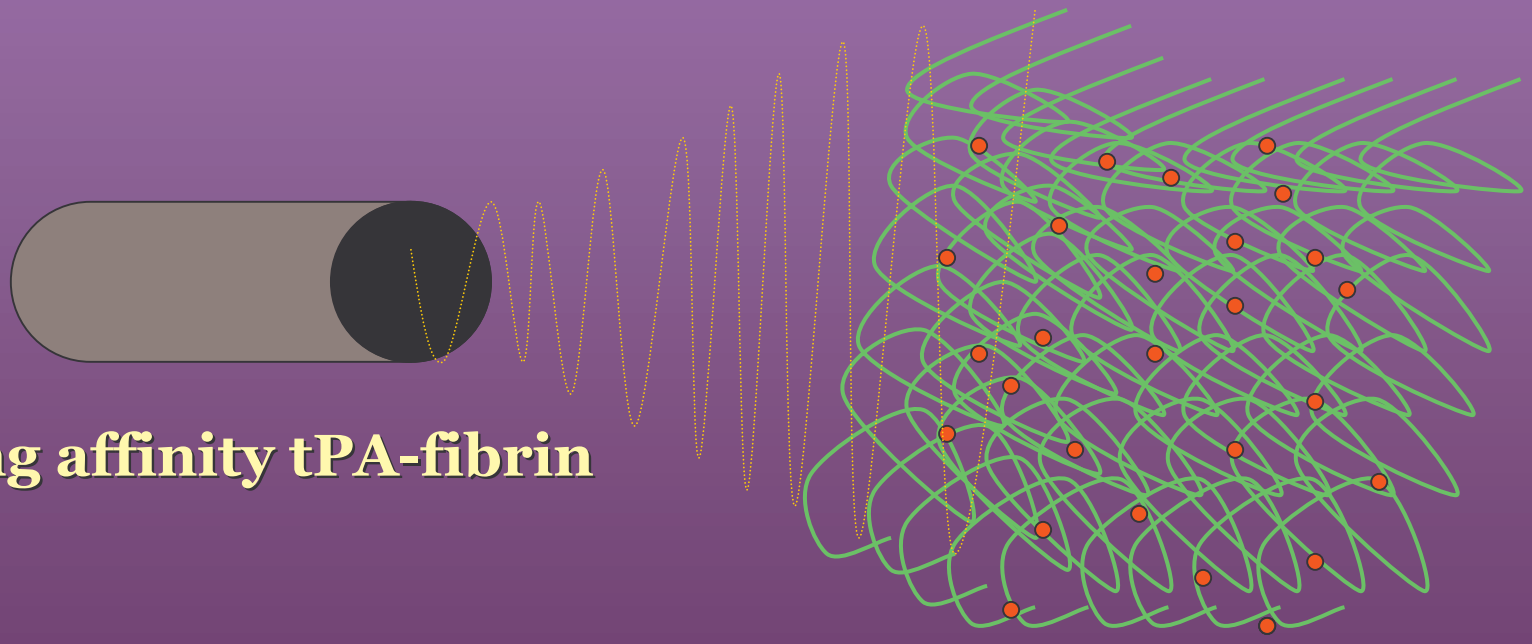




Flow turbolences surrounding the thrombus: microstreaming

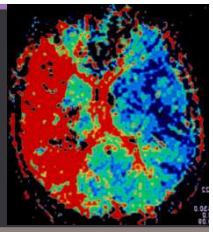
Sonothrombolysis
Better tPA penetration and distribution

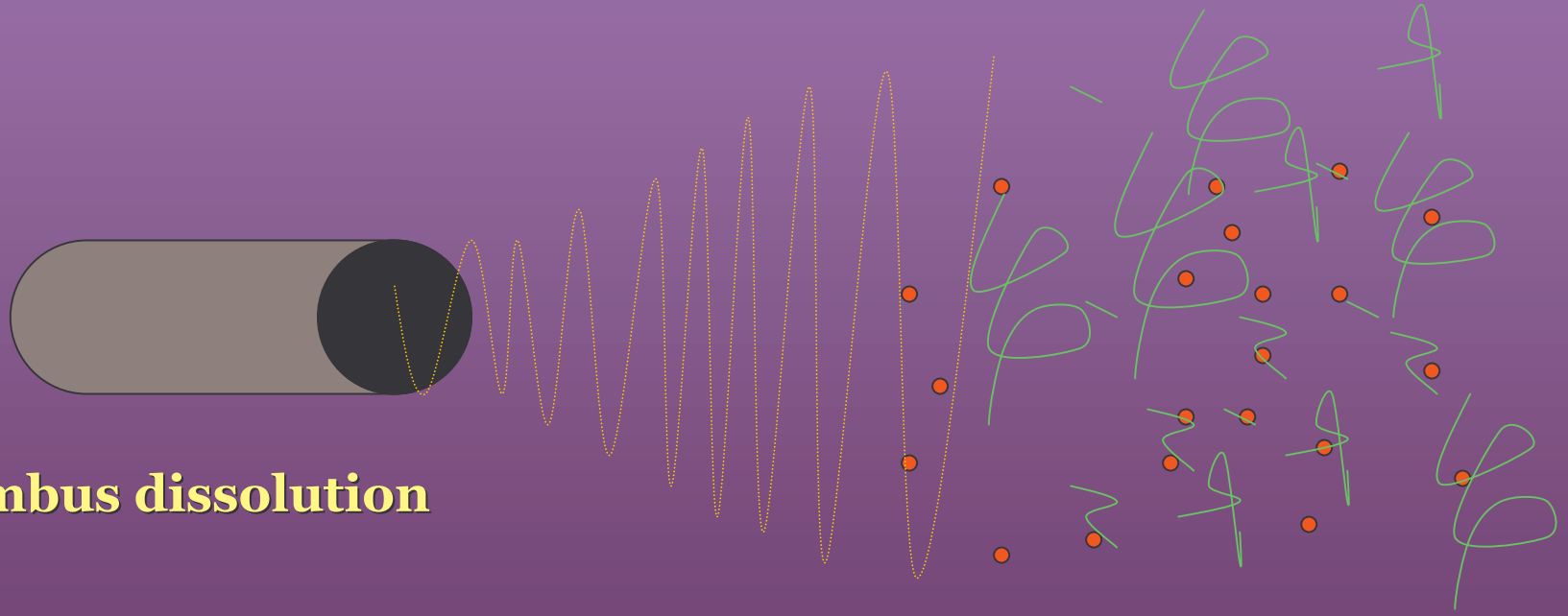




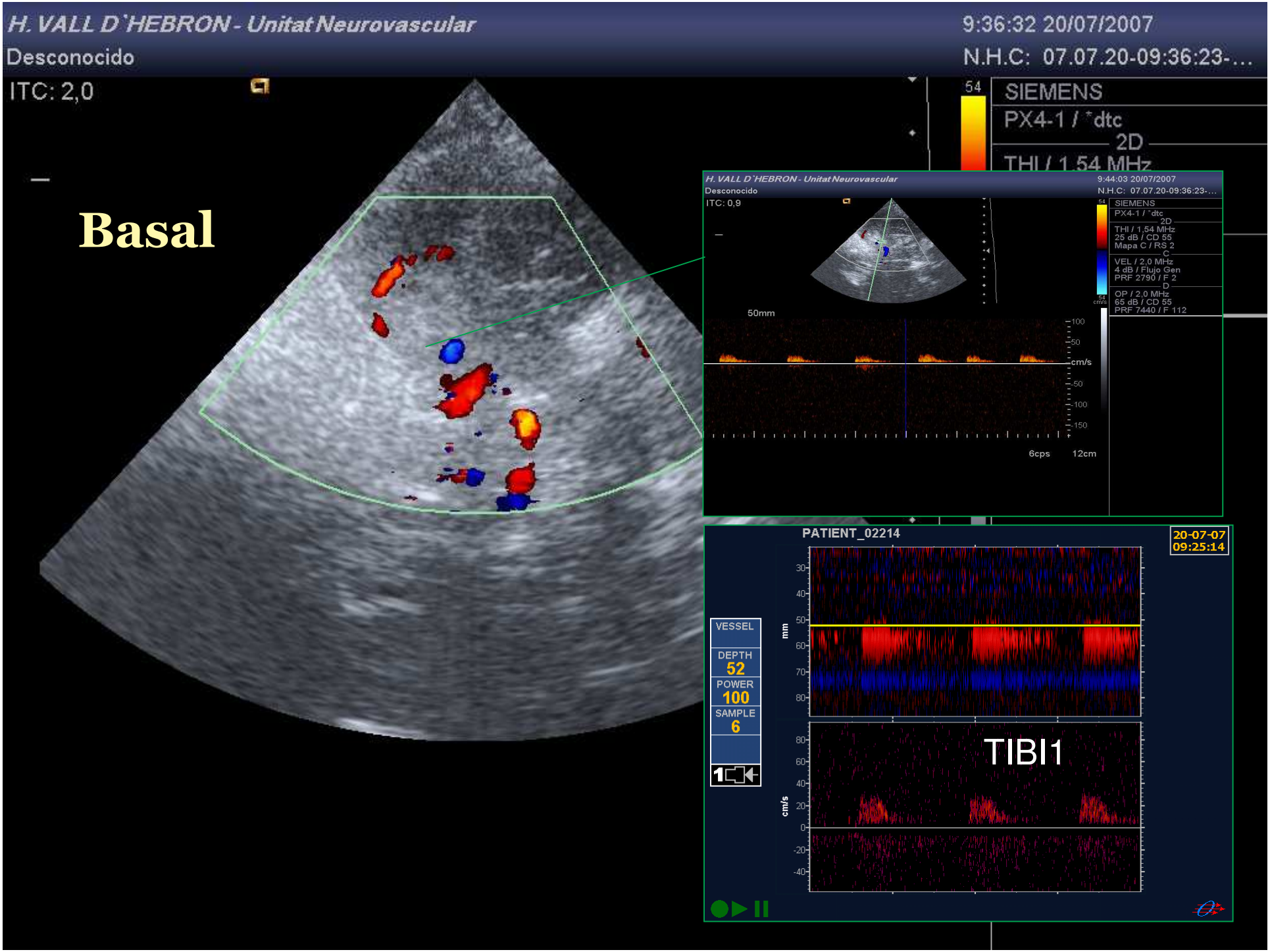
Binding affinity tPA-fibrin

Sonothrombolysis
Better tPA penetration and distribution





Thrombus dissolution


H. VALL D`HEBRON - Unitat Neurovascular
Desconocido
9:36:32 20/07/2007
N.H.C: 07.07.20-09:36:23-...
ITC: 2,0
54
SIEMENS
PX4-1 / *dtc
2D
THI / 1,54 MHz
Basal
H. VALL D`HEBRON - Unitat Neurovascular
Desconocido
9:44:03 20/07/2007
N.H.C: 07.07.20-09:36:23-...
ITC: 0,9
SIEMENS
PX4-1 / *dtc
2D
THI / 1,54 MHz
25 dB / CD 55
Mapa C / RS 2
C
VEL / 2,0 MHz
4 dB / Flujo Gen
PRF 2790 / F 2
D
OP / 2,0 MHz
65 dB / CD 55
PRF 7440 / F 112
50mm
100
50
cm/s
50
100
150
6cps
12cm
PATIENT_02214
20-07-07
09:25:14
VESSEL
DEPTH
52
POWER
100
SAMPLE
6
mm
30
40
50
60
70
80
TIBI1
cm/s
80
60
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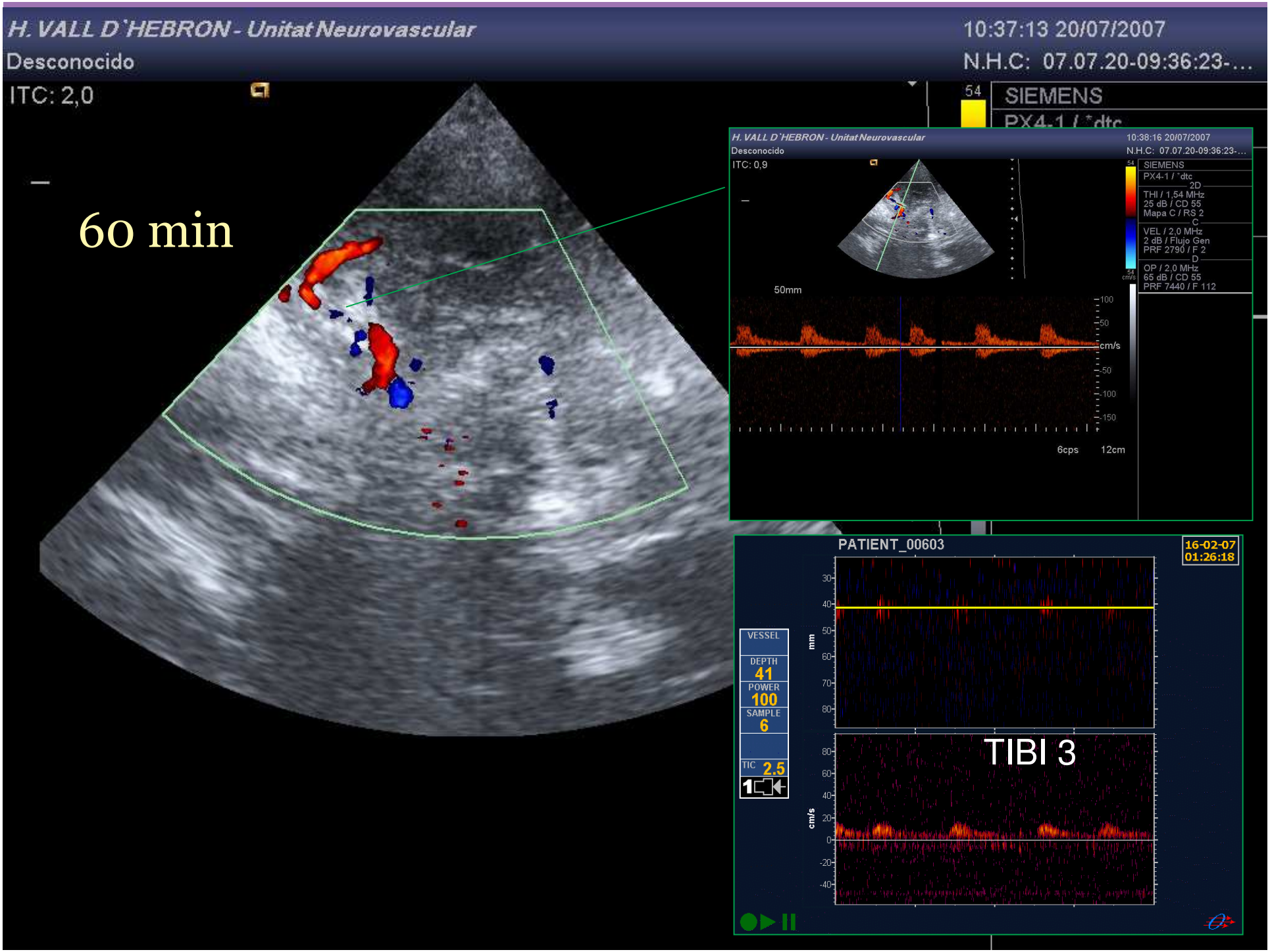
20
0
-20
-40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54
SIEMENS
60 min
H. VALL D`HEBRON - Unitat Neurovascular
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ITC: 0,9
SIEMENS
PX4-1 / *dtc
2D
THI / 1,54 MHz
25 dB / CD 55
Mapa C / RS 2
C
VEL / 2,0 MHz
2 dB / Flujo Gen
PRF 2790 / F 2
D
OP / 2,0 MHz
65 dB / CD 55
PRF 7440 / F 112
50mm
cm/s
6cps
12cm
PATIENT_00603
16-02-07
01:26:18
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POWER
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SAMPLE
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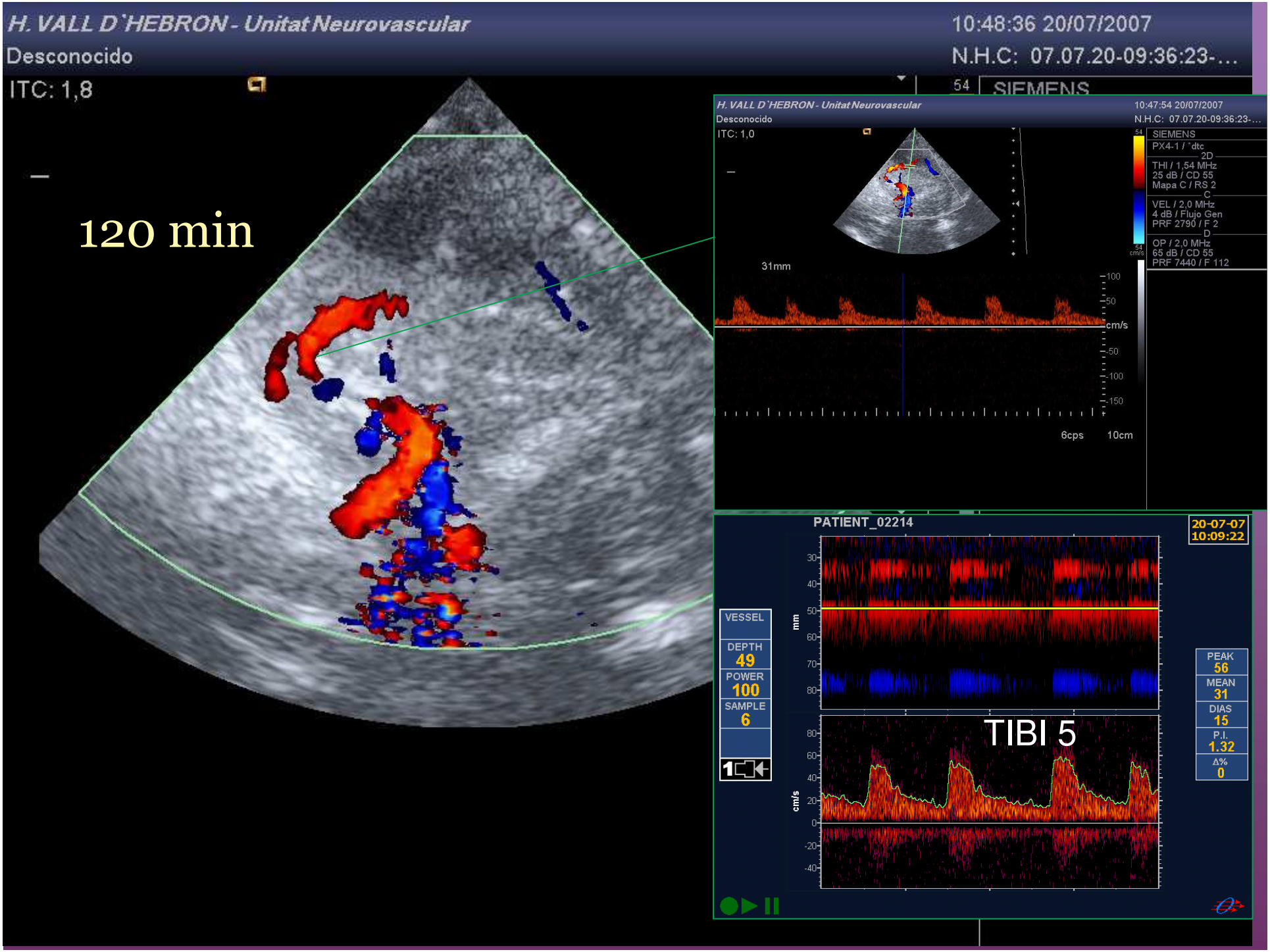
TIC
2.5
mm
cm/s
TIBI 3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ITC: 1,8
54
SIEMENS
120 min
H. VALL D`HEBRON - Unitat Neurovascular
Desconocido
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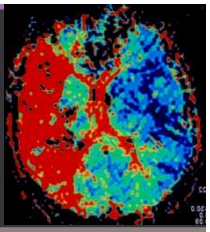
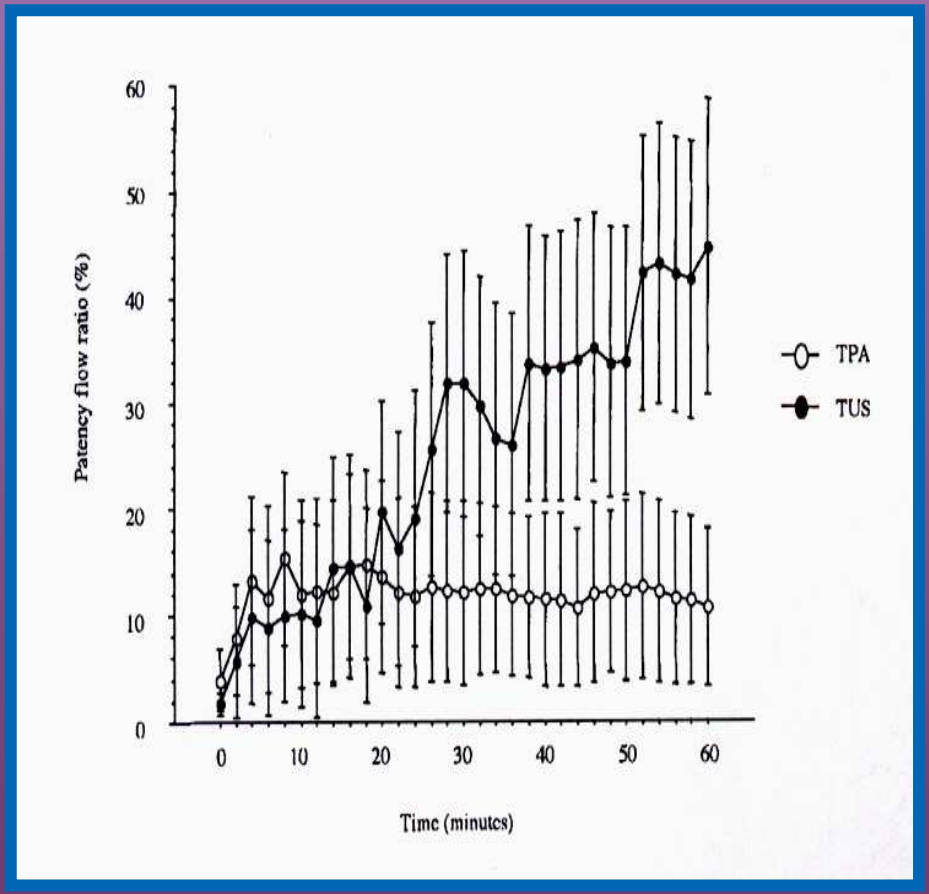
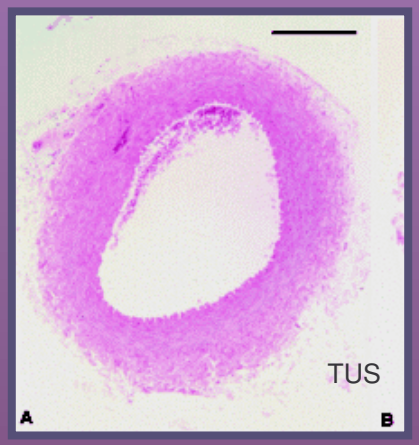
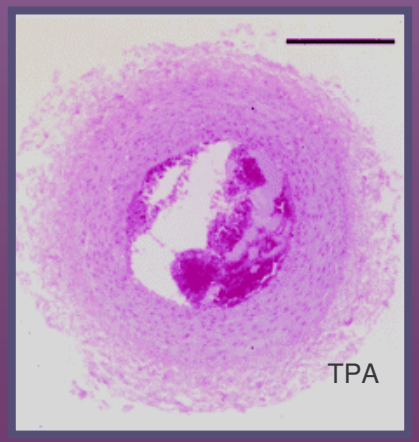
N.H.C: 07.07.20-09:36:23-...
ITC: 1,0
SIEMENS
PX4-1 / dtc
2D
THI / 1,54 MHz
25 dB / CD 55
Mapa C / RS 2
C
VEL / 2,0 MHz
4 dB / Flujo Gen
PRF 2790 / F 2
D
OP / 2,0 MHz
65 dB / CD 55
PRF 7440 / F 112
31mm
cm/s
6cps
10cm
PATIENT_02214
20-07-07
10:09:22
VESSEL
DEPTH
49
POWER
100
SAMPLE
6
mm
cm/s
TIBI 5
PEAK
56
MEAN
31
DIAS
15
P.I.
1.32
Δ%
0

Ultrasound Enhanced Thrombolysis Animal models



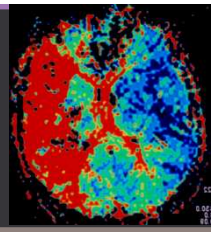


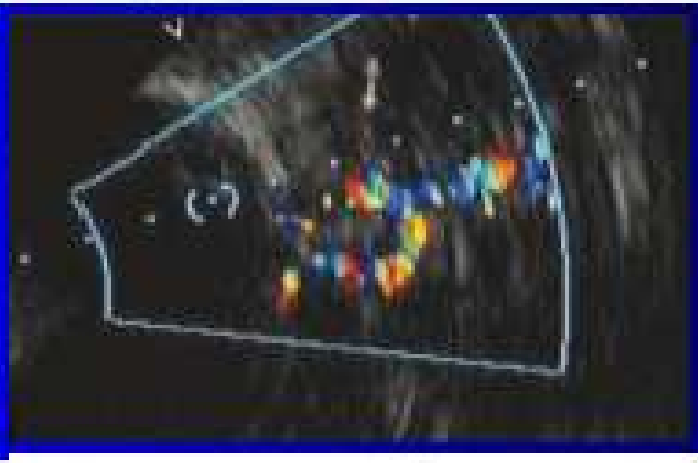
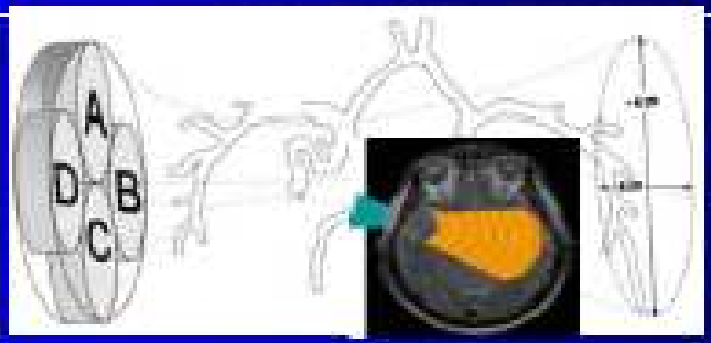




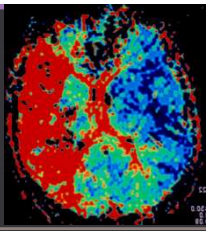
Ishibashi y cols Stroke 2002

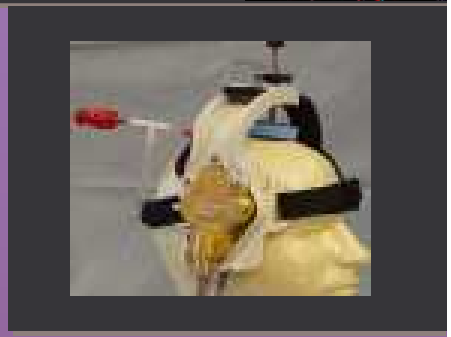
US-enhanced thrombolysis in acute stroke



Trial	Transducer	Tissues Exposed	sICH	CR	mRS 0-1
CLOTBUST n = 126 2 MHz single beam			4.8%	38%	42%
			completed		
Eggers et al. n = 25 2-4MHz multi-beam			18%	27%	27%
			no pre-determined sample size		
TRUMBI n = 26 300 KHz multi-beam			36%	<22%	?
			terminated		

TRUMBI trial

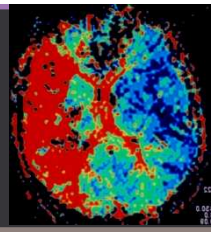


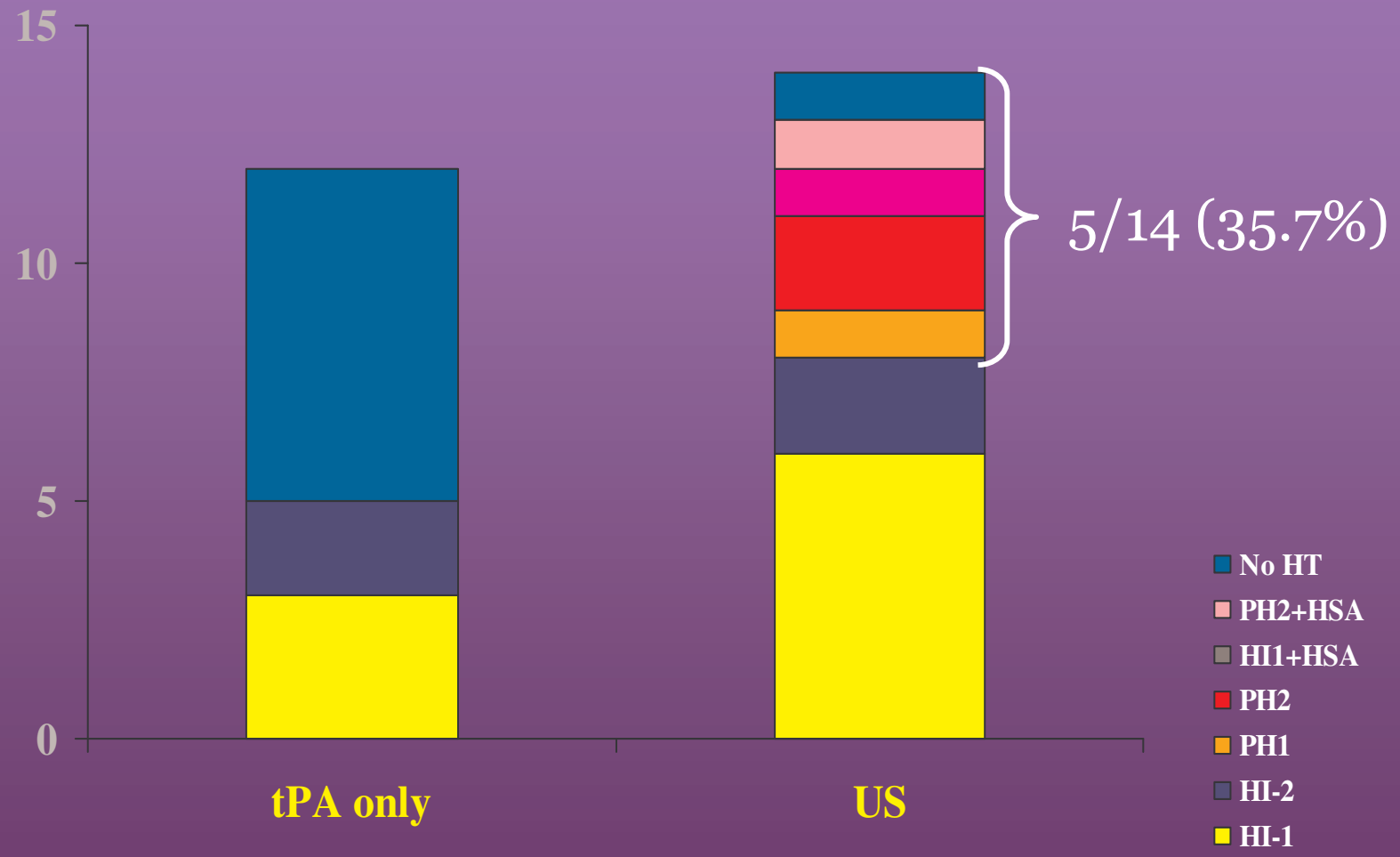


- Randomized trial of 26 patients < 6h
- Low-frequency high intensity US during 90 minutes
  - 300 Khz
  - 7 W/cm²
  - Mechanical Index <0.2
  - Thermal index <0.5
- Stopped. SICH
  - 5/14 (42%) tPA + US

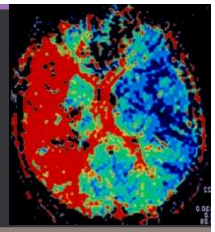
Daffertshofer *Stroke* 2005

TRUMBI trial
Intracranial hemorrhage





Daffershofer *Stroke* 2005

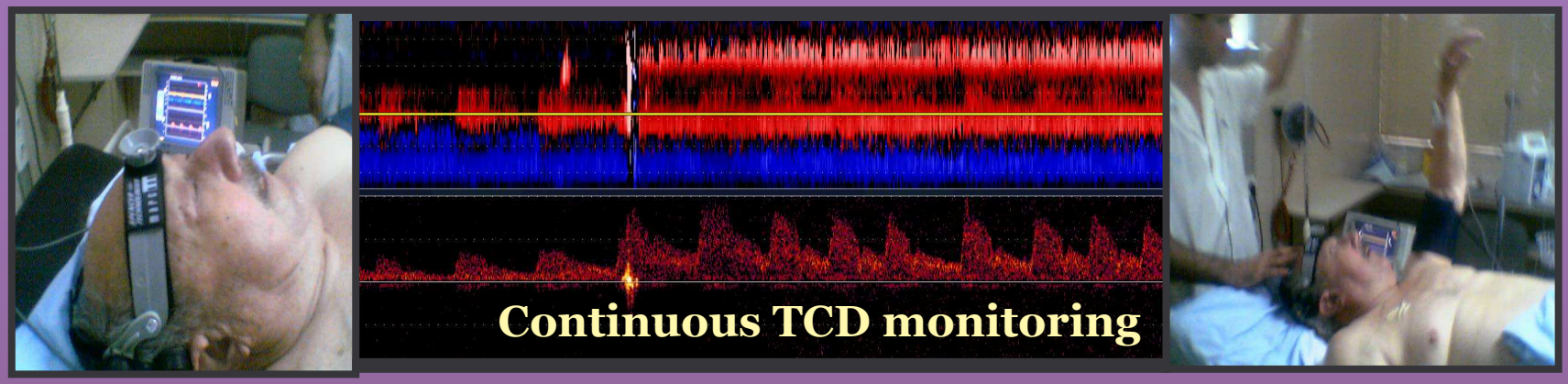


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

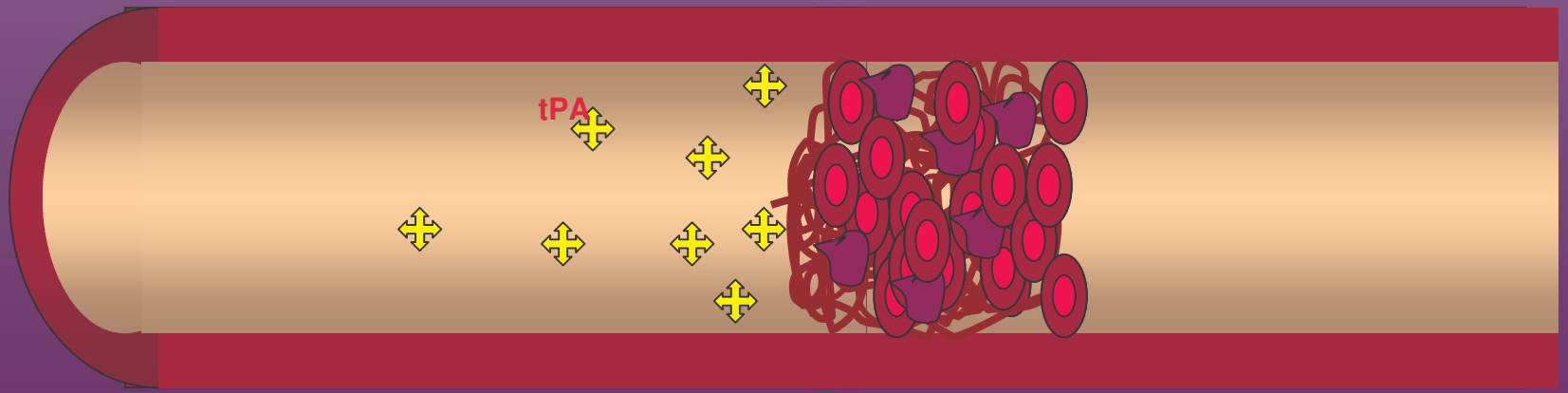
Ultrasound-Enhanced Systemic Thrombolysis for Acute Ischemic Stroke

Andrei V. Alexandrov, M.D., Carlos A. Molina, M.D., James C. Grotta, M.D., Zsolt Garami, M.D., Shiela R. Ford, R.N., Jose Alvarez-Sabin, M.D., Joan Montaner, M.D., Maher Saqqur, M.D., Andrew M. Demchuk, M.D., Lemuel A. Moyé, M.D., Ph.D., Michael D. Hill, M.D., and Anne W. Wojner, Ph.D., for the CLOTBUST Investigators*

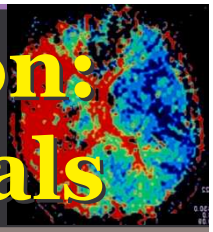


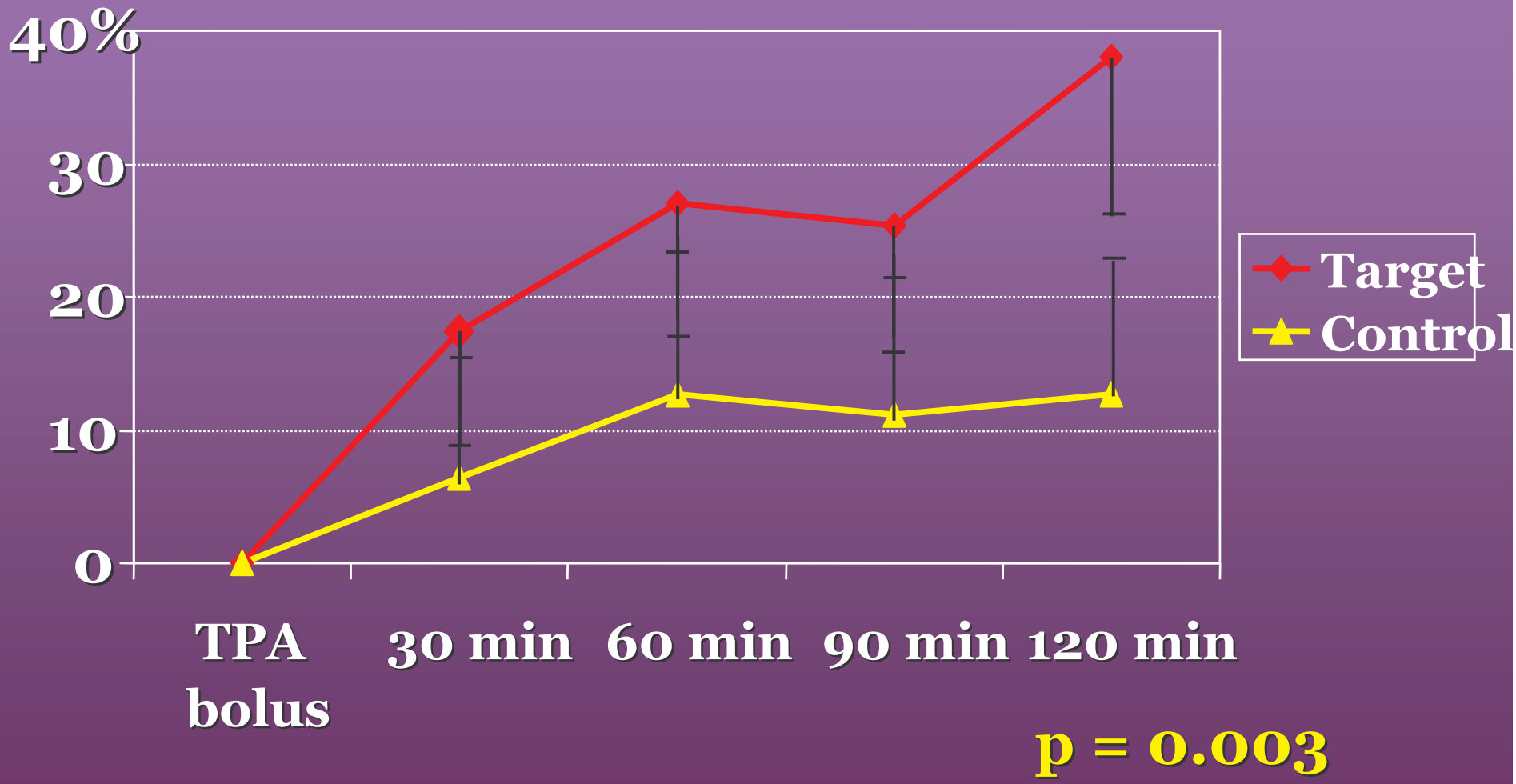
CLOTBUST trial has demonstrated that diagnostic TCD (2 Mhz frequency) increase recanalization rates in acute stroke patients treated with t-PA

Alexandrov et al. *NEJM* 2004



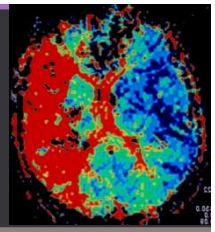
Sustained Complete Recanalization: TCD TIBI 5 Flow at 30 min Intervals





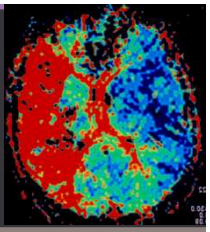
p = 0.003

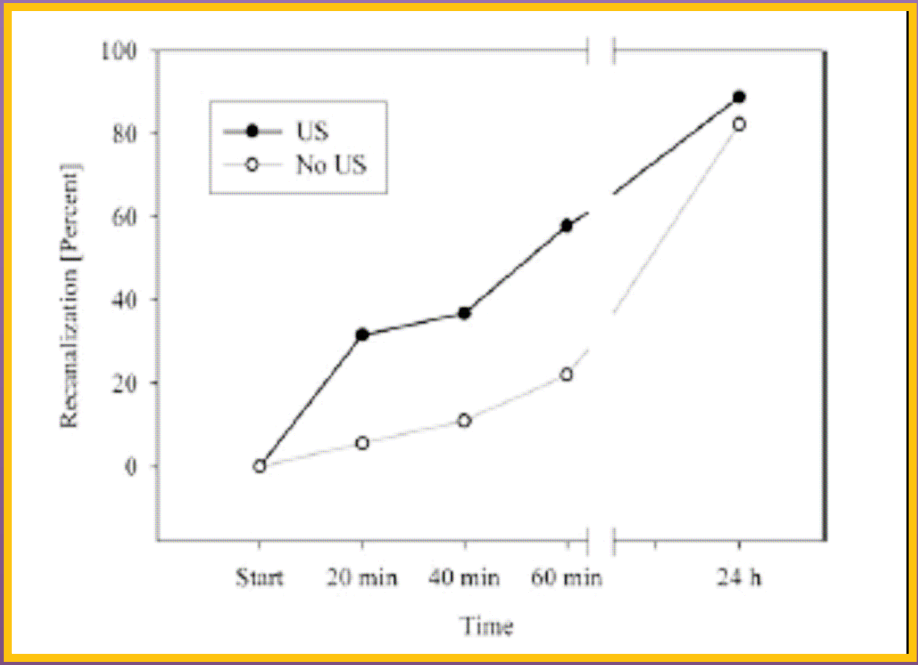
CLOTBUST Limitations

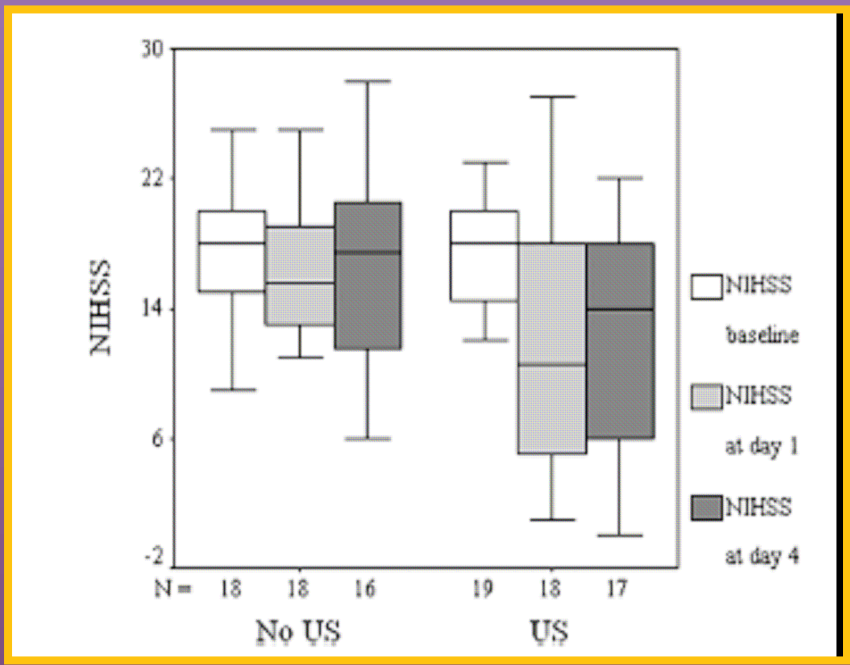


- Unblinded sonographers
- Lack of confirmation of occlusion and recanalization with CTA or MRA
- Sample size was not powered to assess clinical outcome

TCCS-enhanced thrombolysis







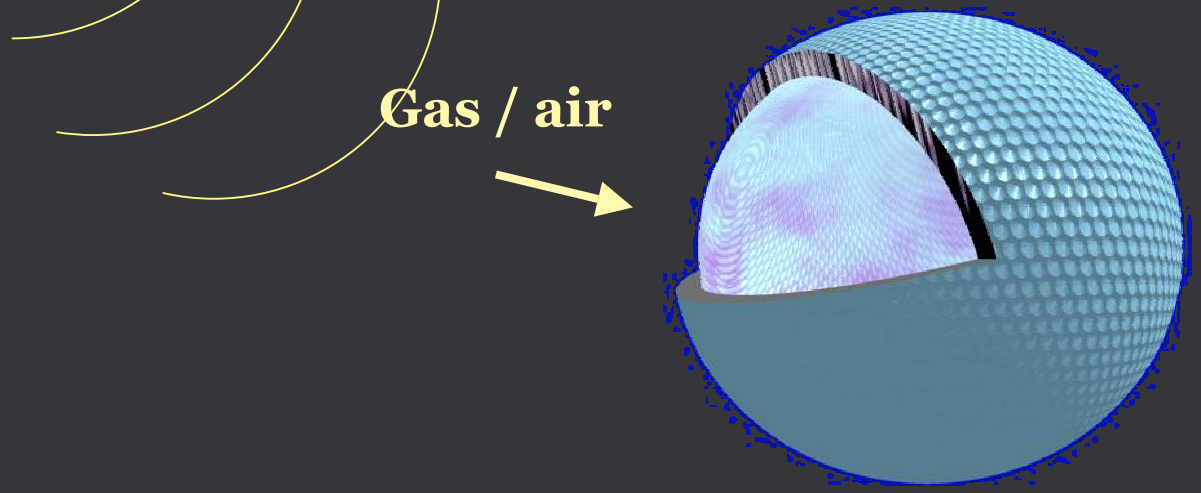
37 patients tPA treated:

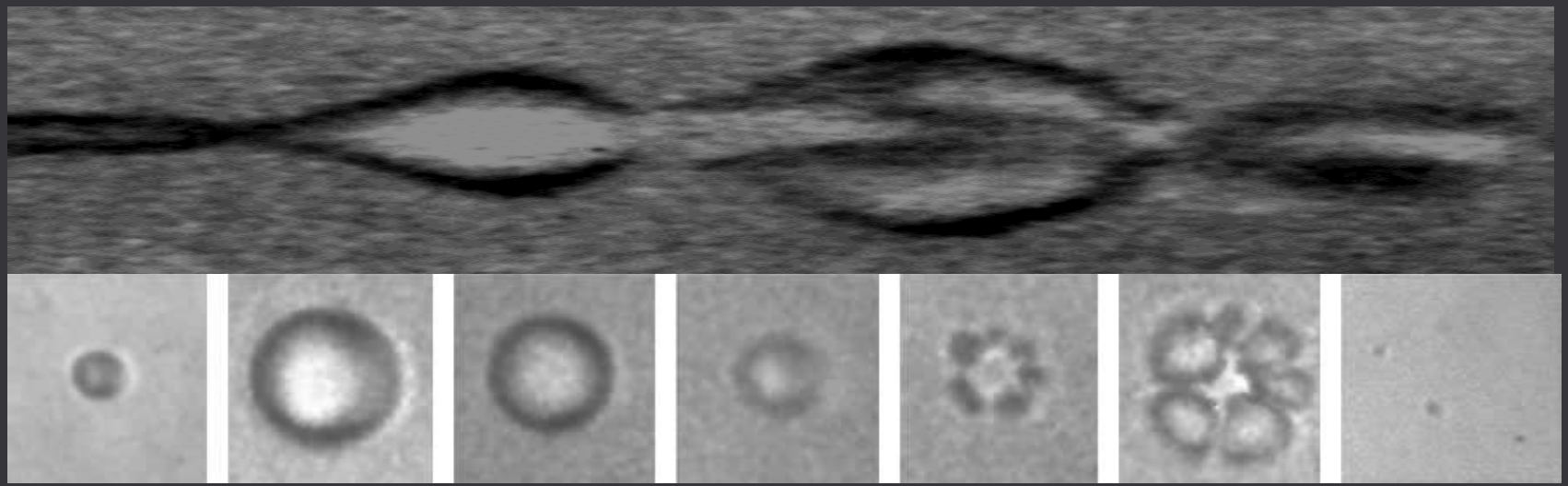
19 US group
tPA + 1 hr TCCS

18 noUS group
tPA

Eggers et al Stroke 2008

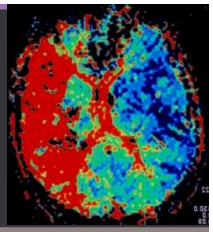
Microbubbles



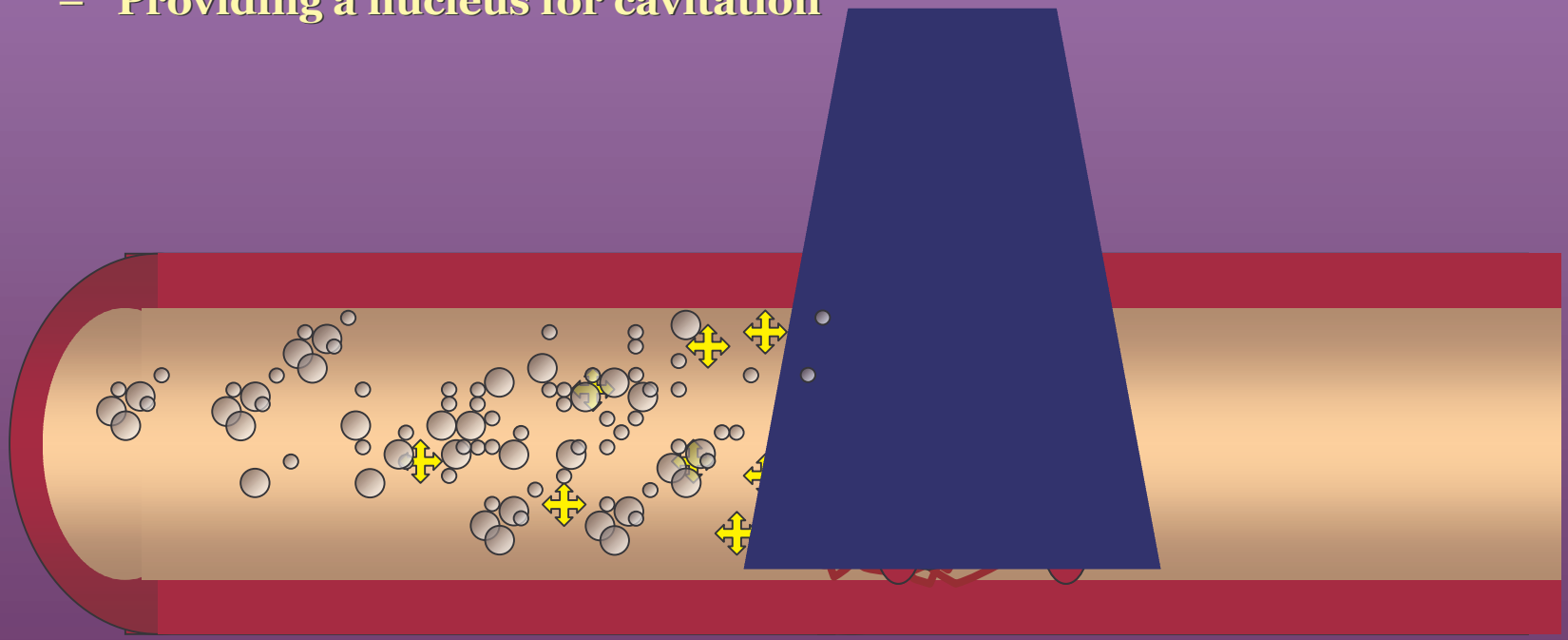


Ferrara K *et al.* UC-Davis

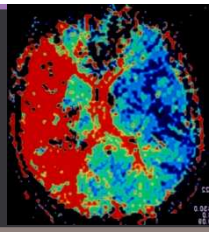
MB-enhanced sonothrombolysis

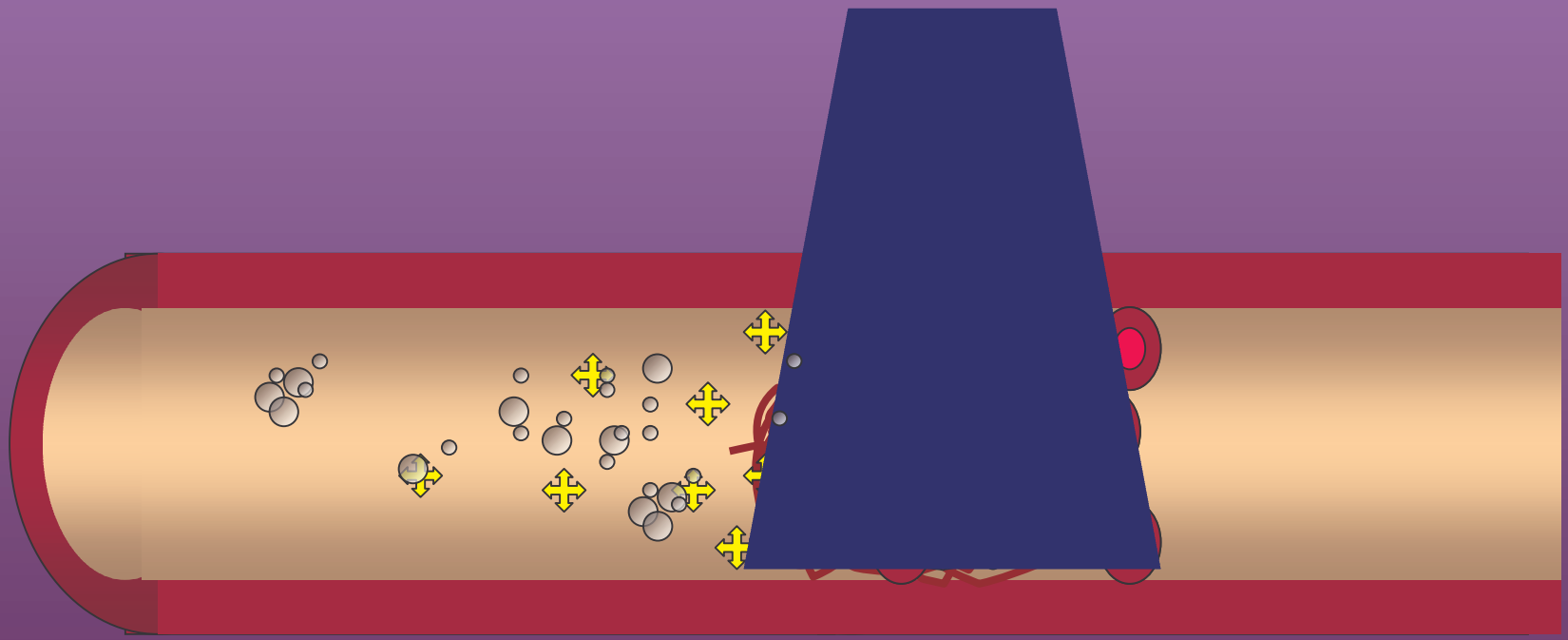


- **Ultrasound-accelerated thrombolysis may be further enhanced by MB**
  - **lowering the threshold for cavitation**
  - **Providing a nucleus for cavitation**

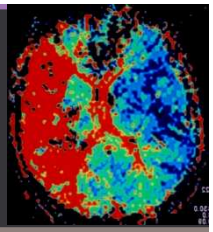


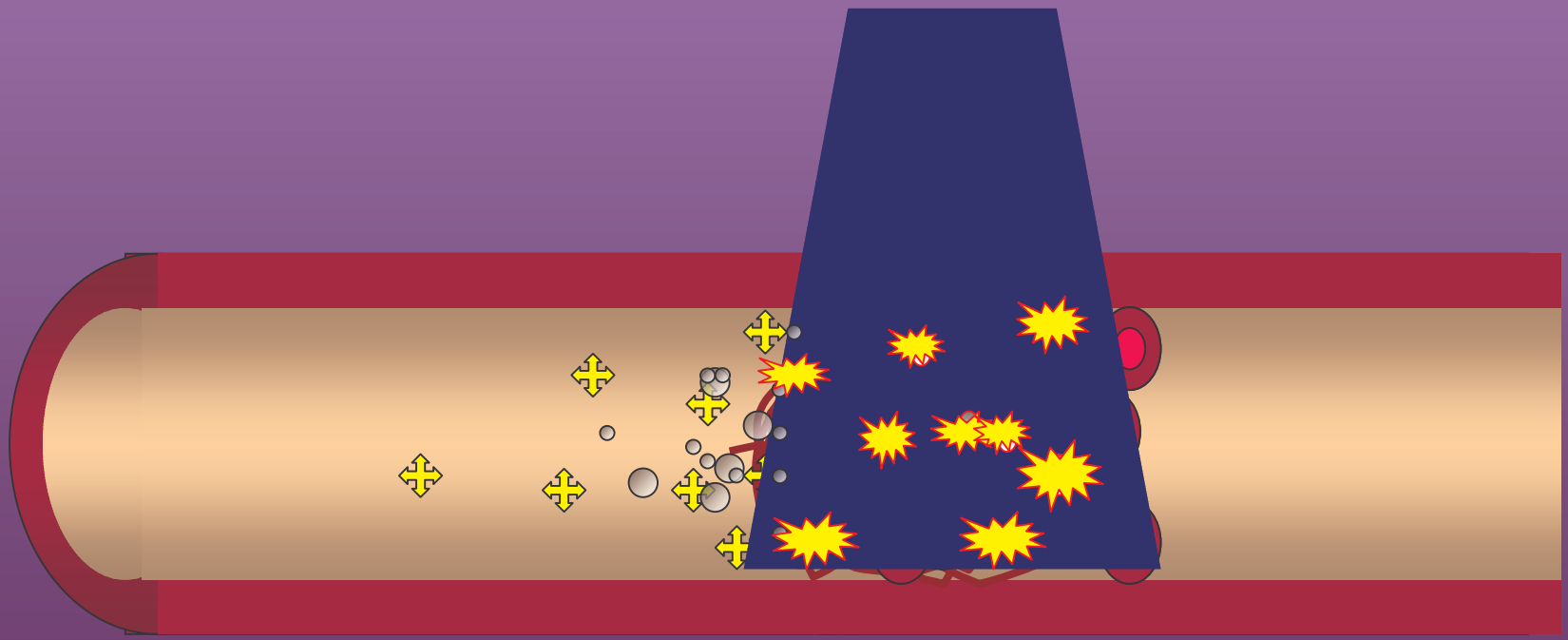
MB-enhanced sonothrombolysis



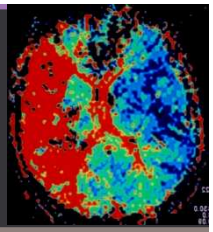


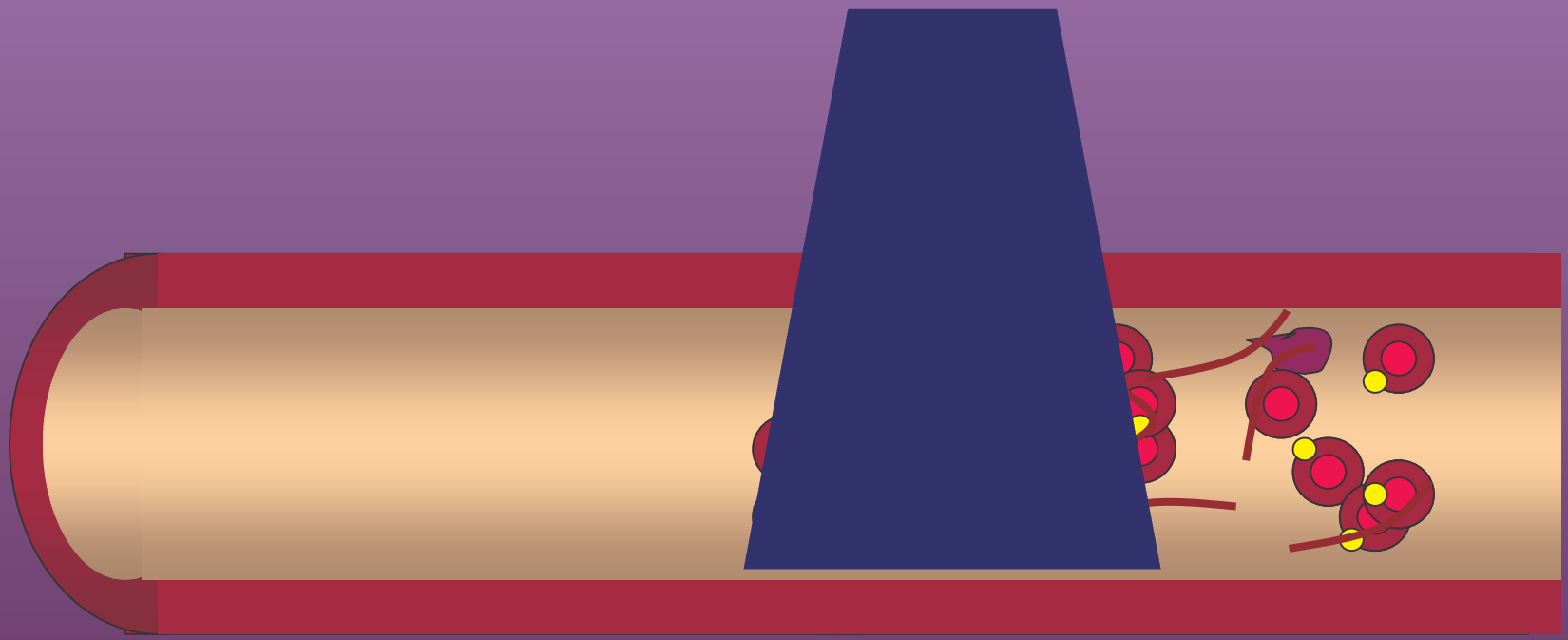
MB-enhanced sonothrombolysis

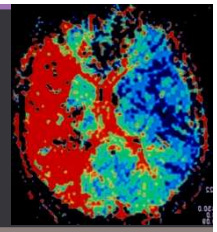




MB-enhanced sonothrombolysis





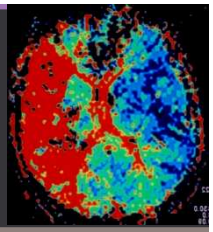


Microbubble Administration Accelerates Clot Lysis During Continuous 2-MHz Ultrasound Monitoring in Stroke Patients Treated With Intravenous Tissue Plasminogen Activator

Carlos A. Molina, MD, PhD; Marc Ribo, MD, PhD; Marta Rubiera, MD; Joan Montaner, MD, PhD; Esteban Santamarina, MD; Raquel Delgado-Mederos, MD; Juan F. Arenillas, MD, PhD; Rafael Huertas, MD; Francisco Purroy, MD; Pilar Delgado, MD; José Alvarez-Sabín, MD, PhD

Stroke, 2006

Patients and Methods

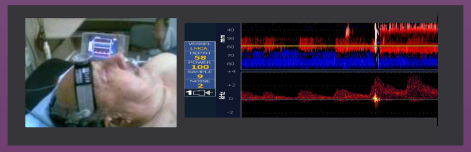


345 ischemic strokes evaluated < 3h

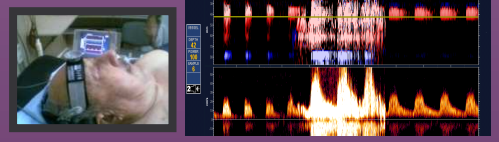
103 patients with MCA occlusion on TCD

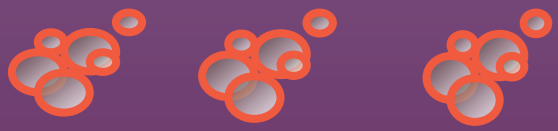
tPA
33%

tPA + US
33%



tPA + US + MB (34%)

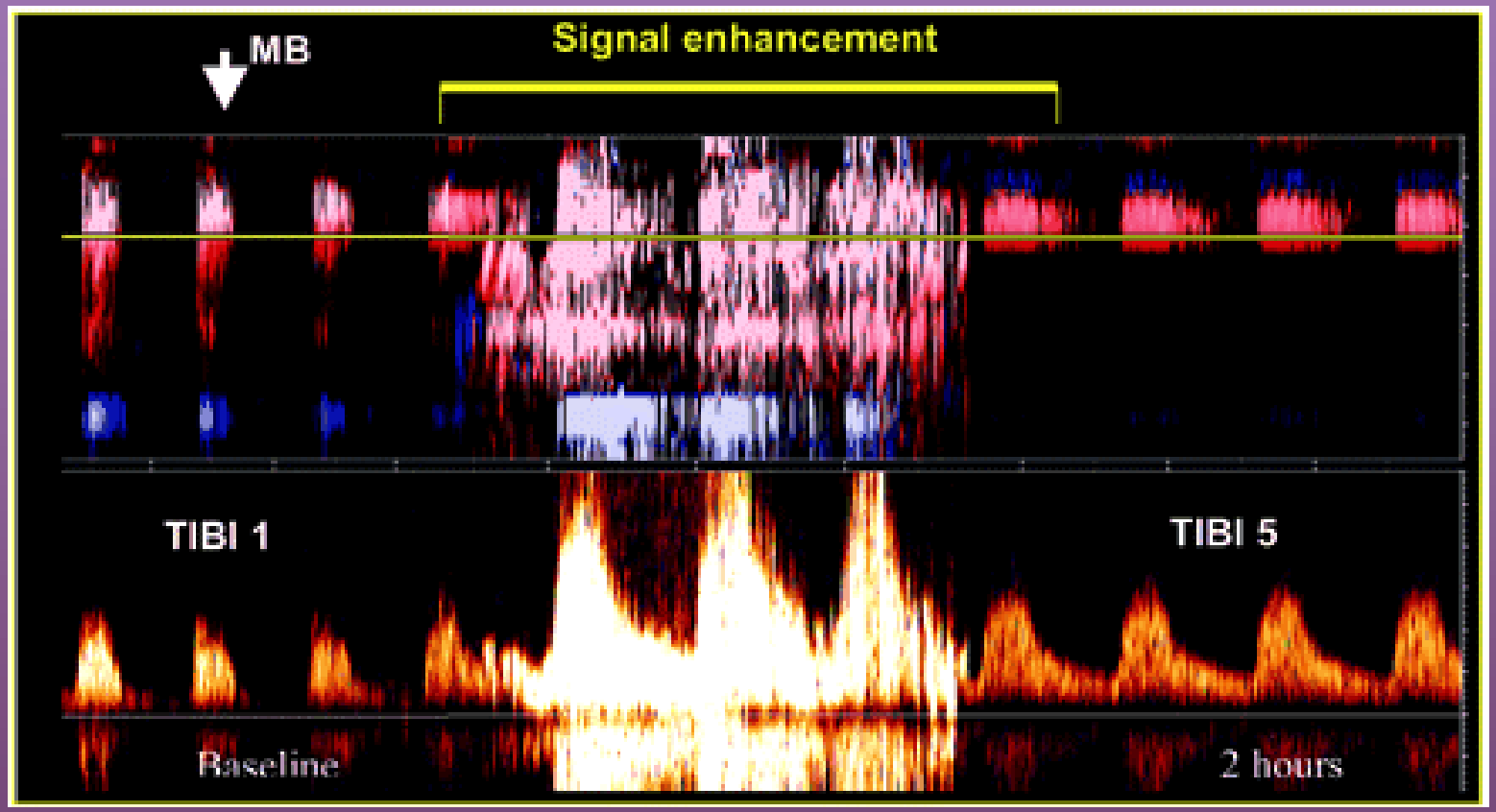




2´ 20´ 40´

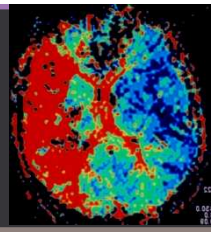
Levovist 400mg/ml

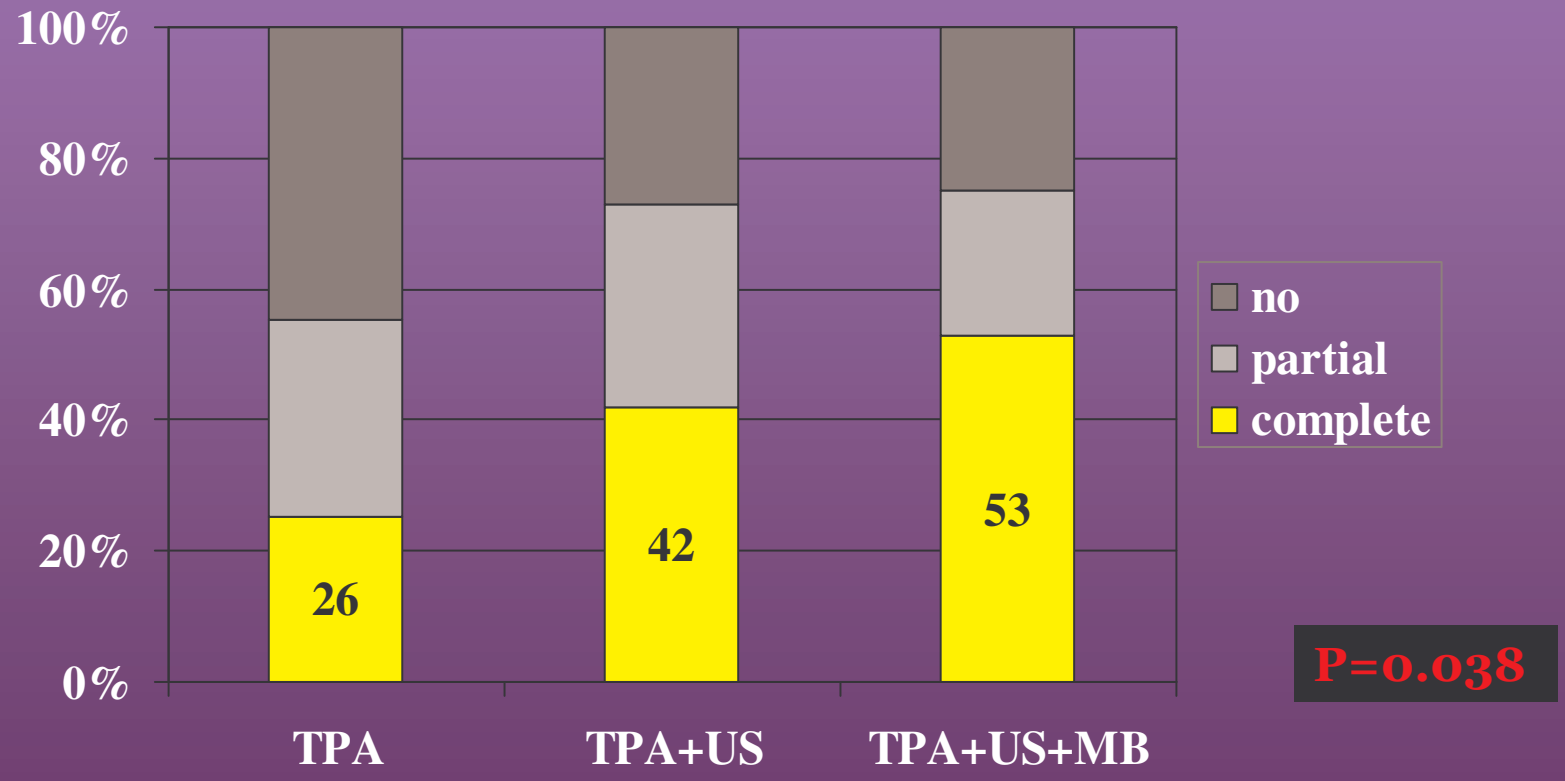
Recanalization after microbubbles



Persistent flow improvement after microbubbles infusion.

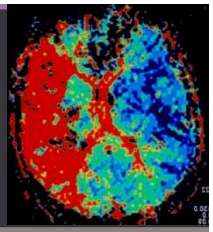
Degree of recanalization



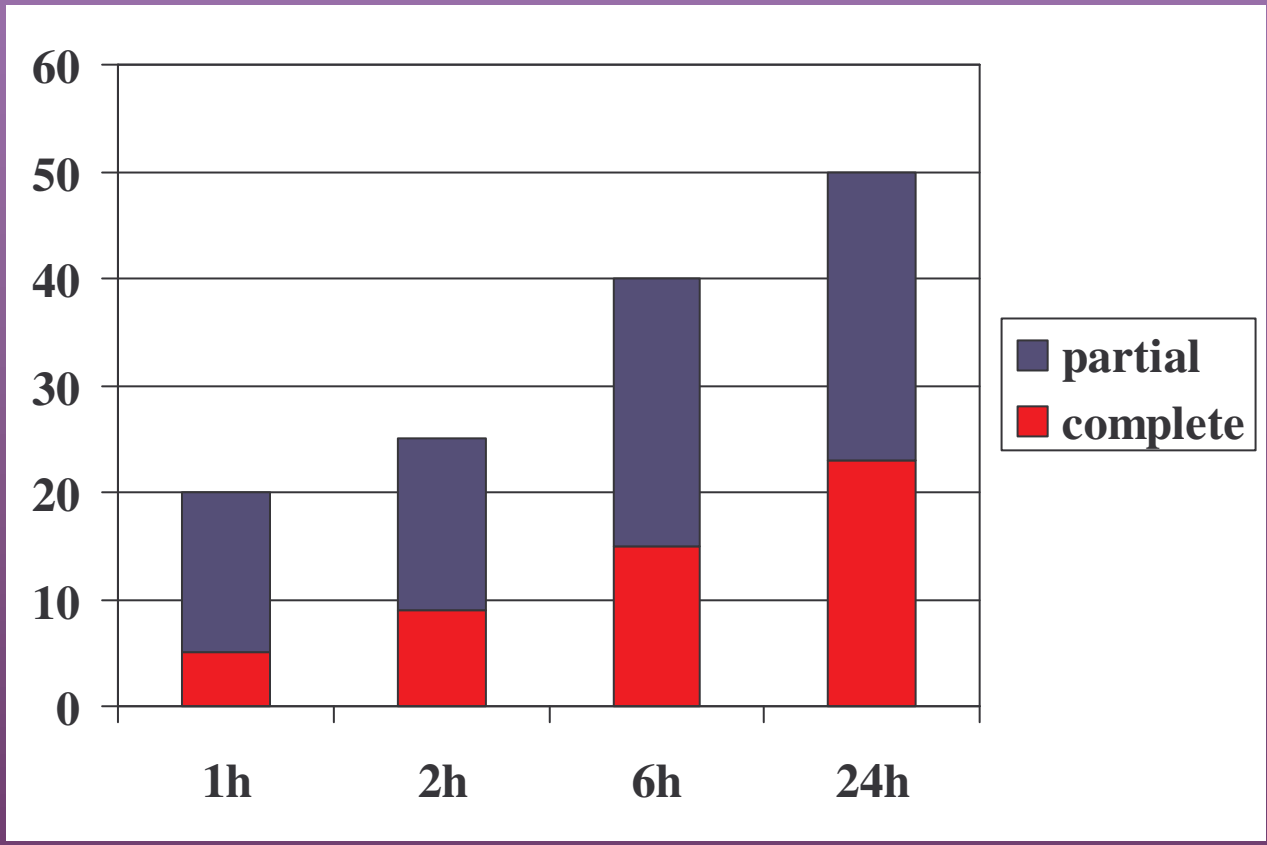


Molina et al *Stroke* 2006

Timing of MB-enhanced recanalization in Basilar Occlusion

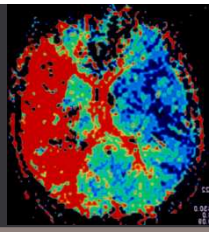


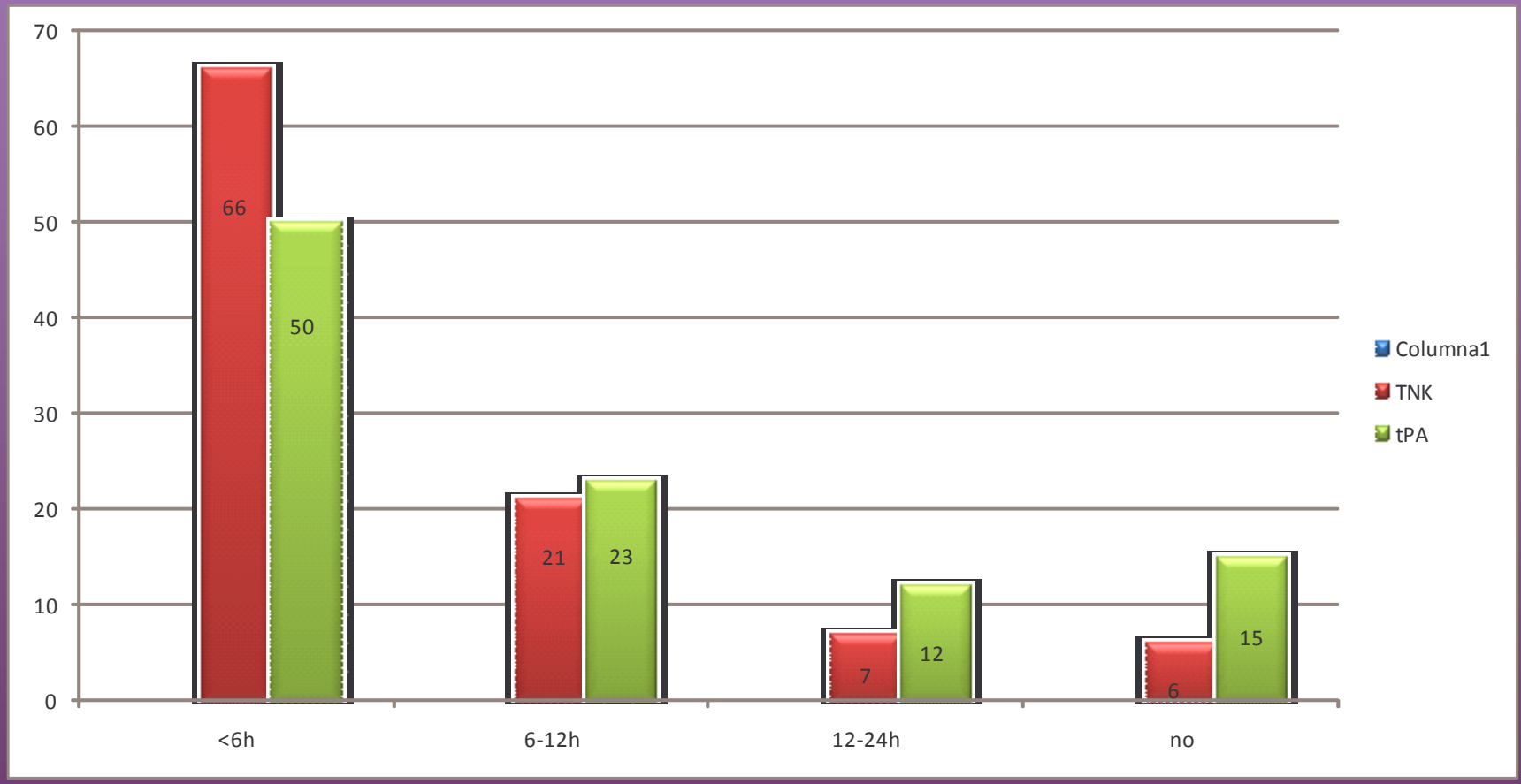
Stroke Unit Vall d´Hebron



Pagola et al. Stroke 2007

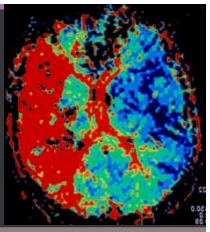
Timing of recanalization after sonothrombolysis with tPA and TNK

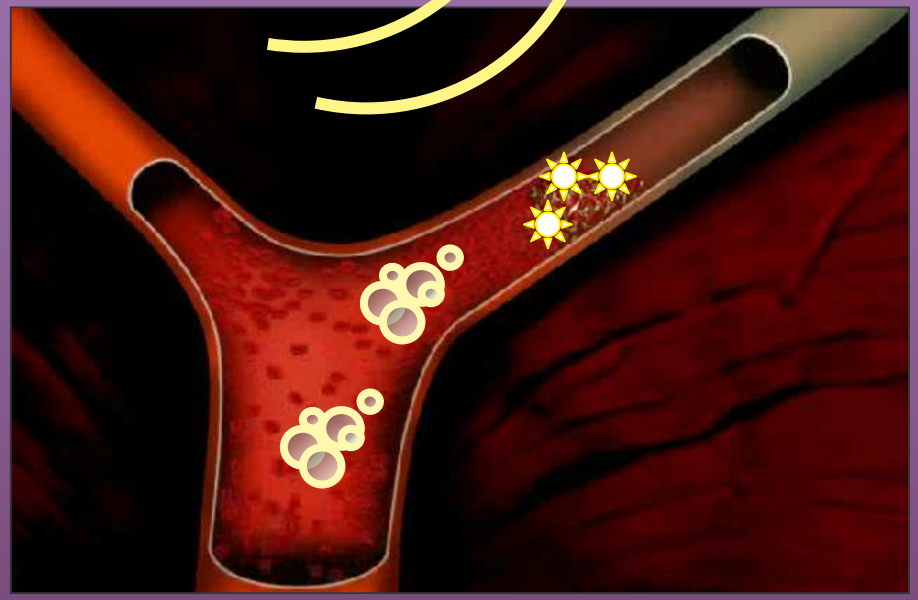


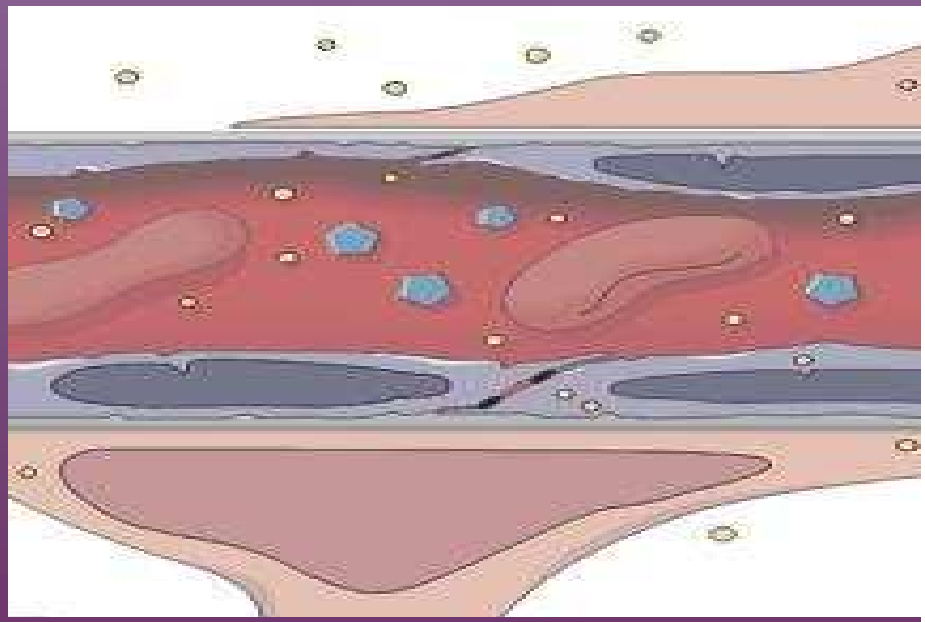


Molina et al ESC 2008

US microbubbles destruction and BBB permeability



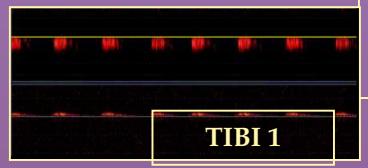




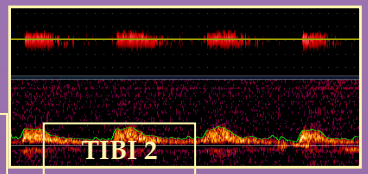
Aim

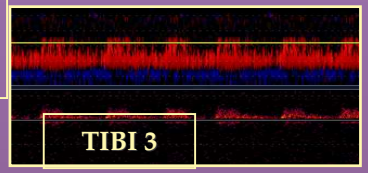
To evaluate the risk of hemorrhagic transformation in acute stroke patients (< 6 h) treated with sonothrombolysis potentiated by microbubbles

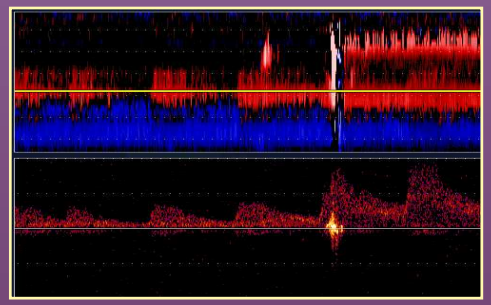
MBs and hemorrhagic transformation



480
Patients with
MCA occlusion

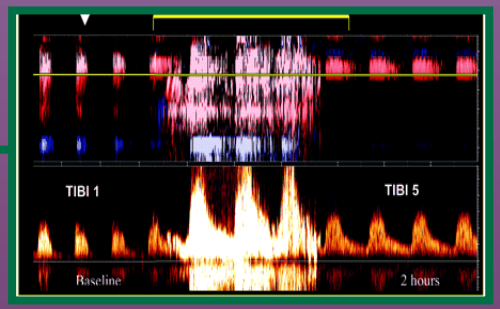






Historical control group

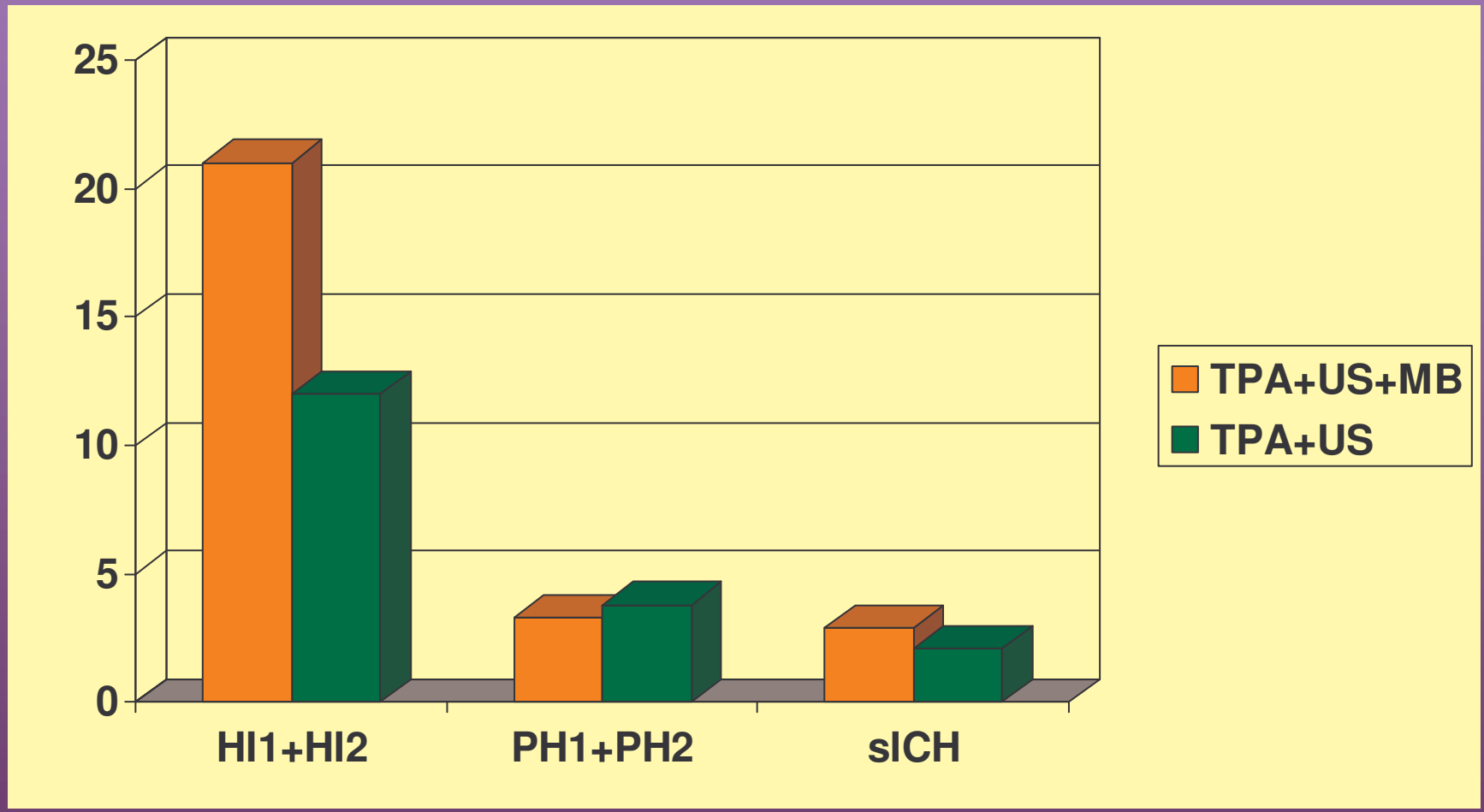
98 patients



MB group (Levovist®)

188 patients

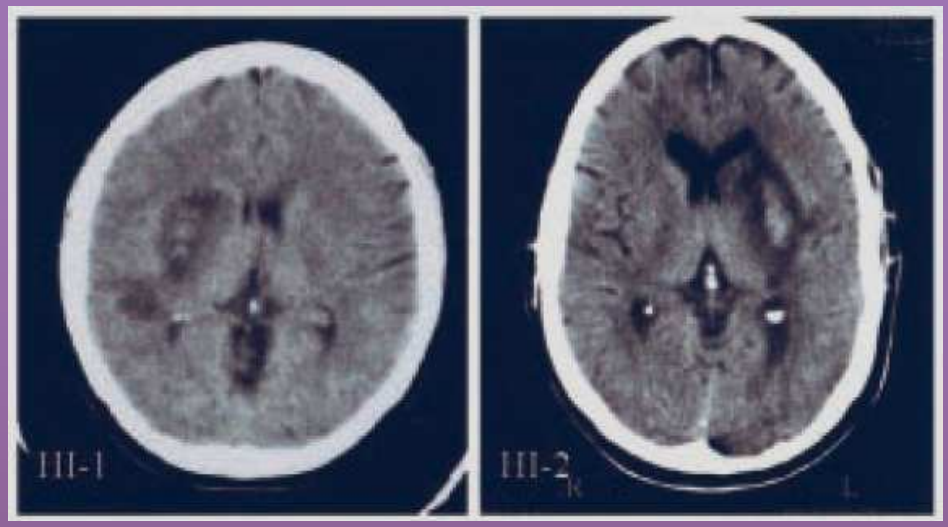
Hemorrhagic transformation



p=0.026
OR 5.8 95% IC 2.1-65

p=0.8

p=0.58

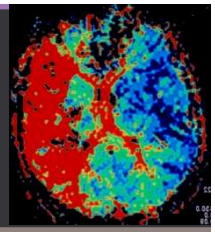


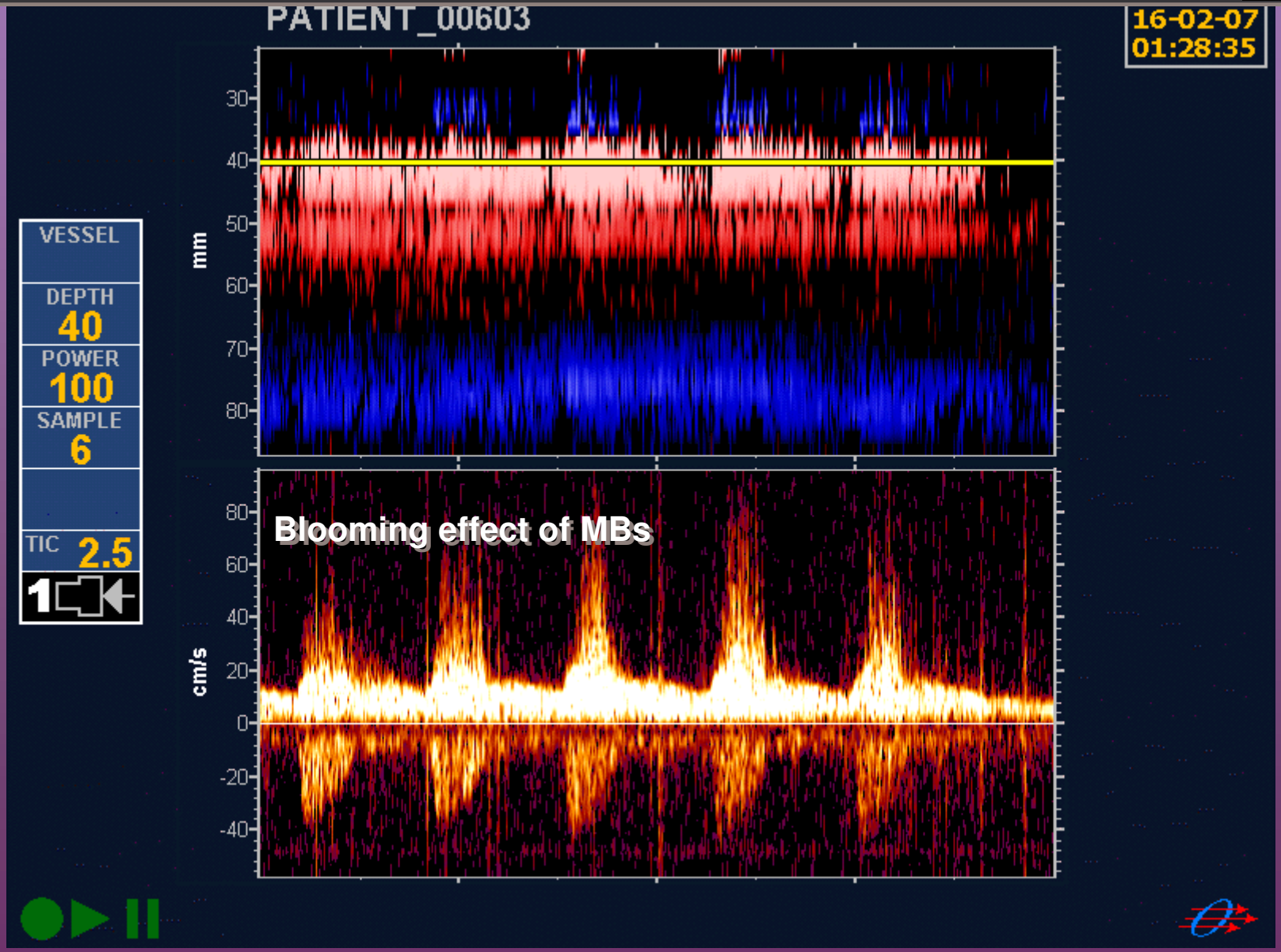
✓MB administration was associated with a higher degree of clinical improvement at 24h and higher rate of HI1-HI2, but it did not increase the risk of symptomatic ICH.

Dinia et al.
International Stroke Conference,
New Orleans, 2008

LMCA occlusion
NIHSS score 12

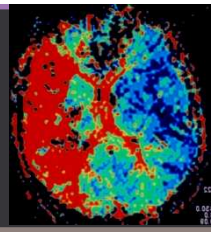
Blooming
Time: 3 min 15 sec

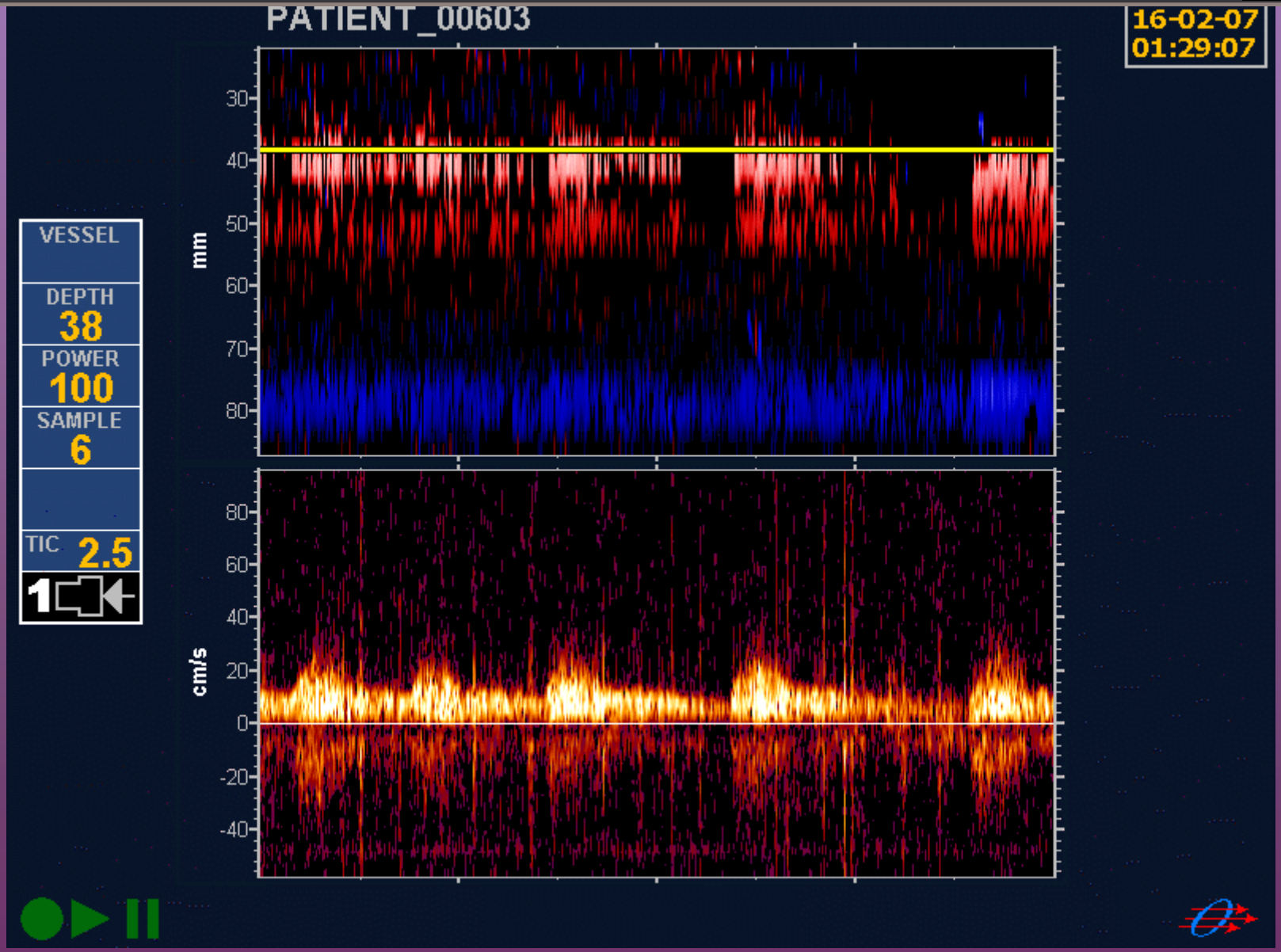




LMCA occlusion
NIHSS score 12

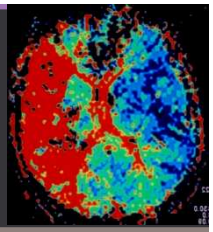
Blooming
Time: 3 min 45 sec

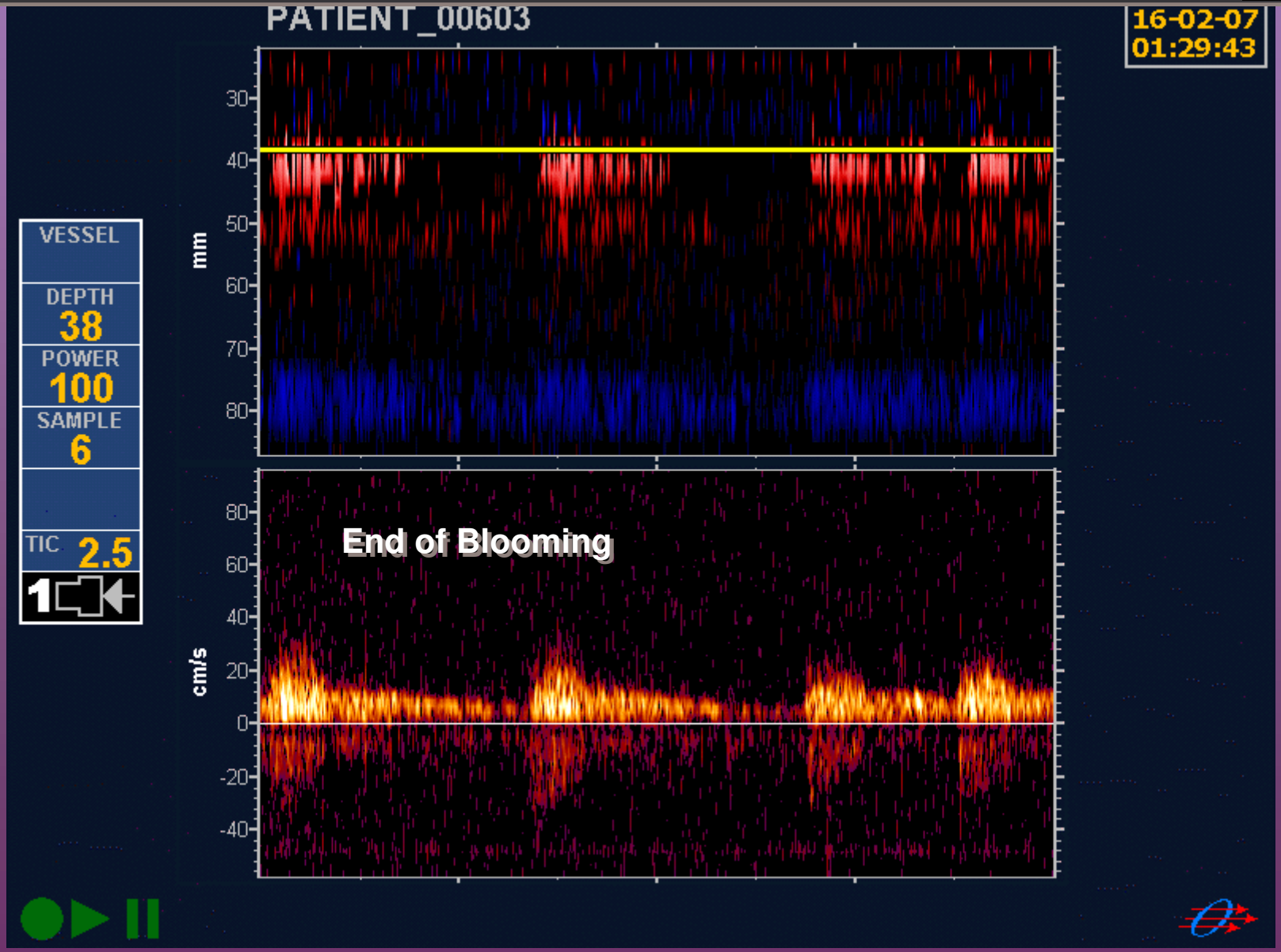




LMCA occlusion
NIHSS score 12

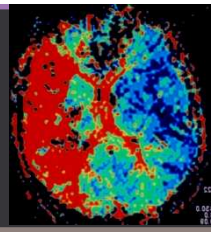
End of Blooming
Time: 4 min 35 sec

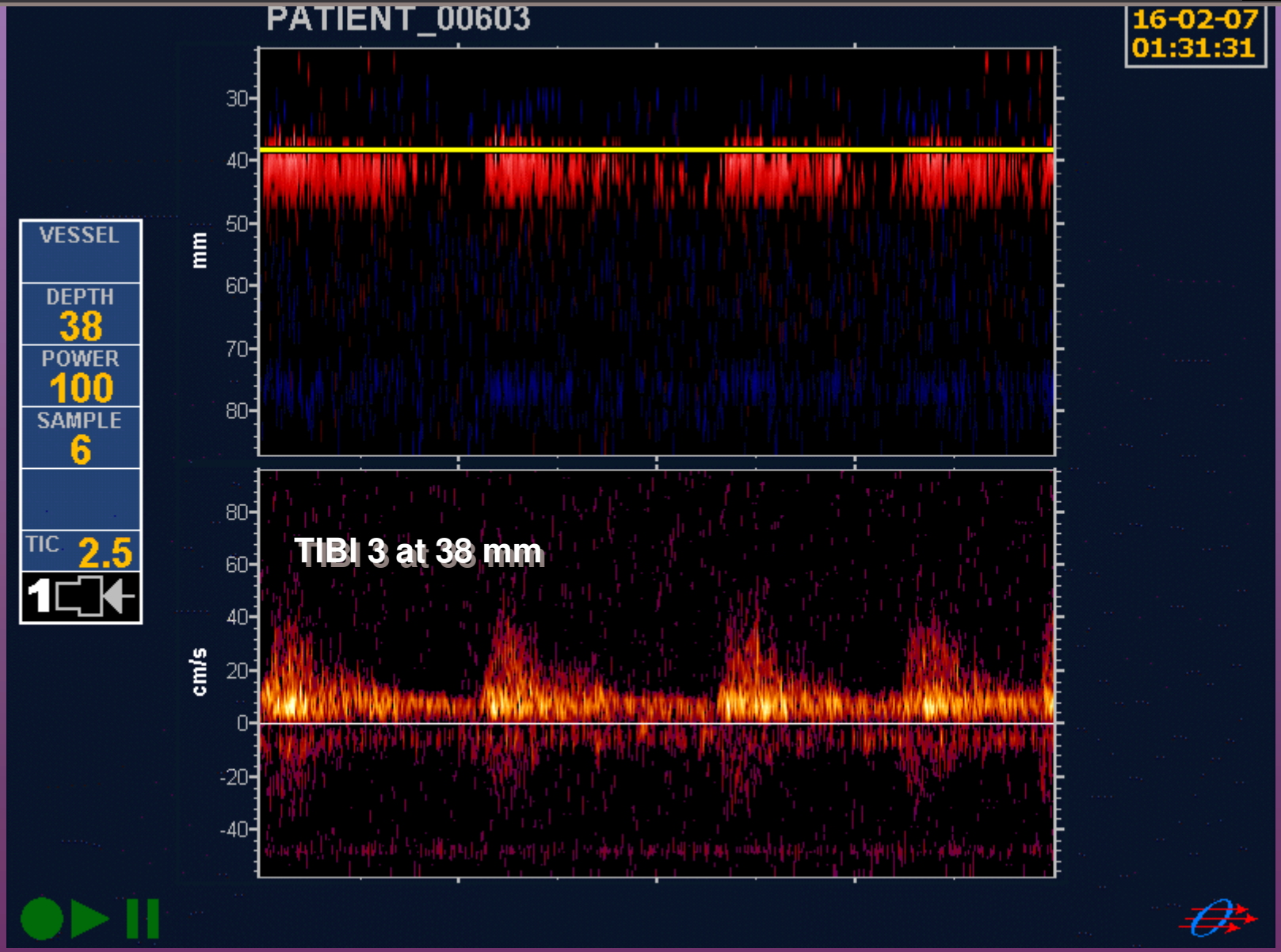




LMCA occlusion
NIHSS score 9

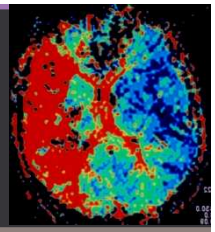
TIBI 3 at 38 mm
Time: 6 min 32 sec

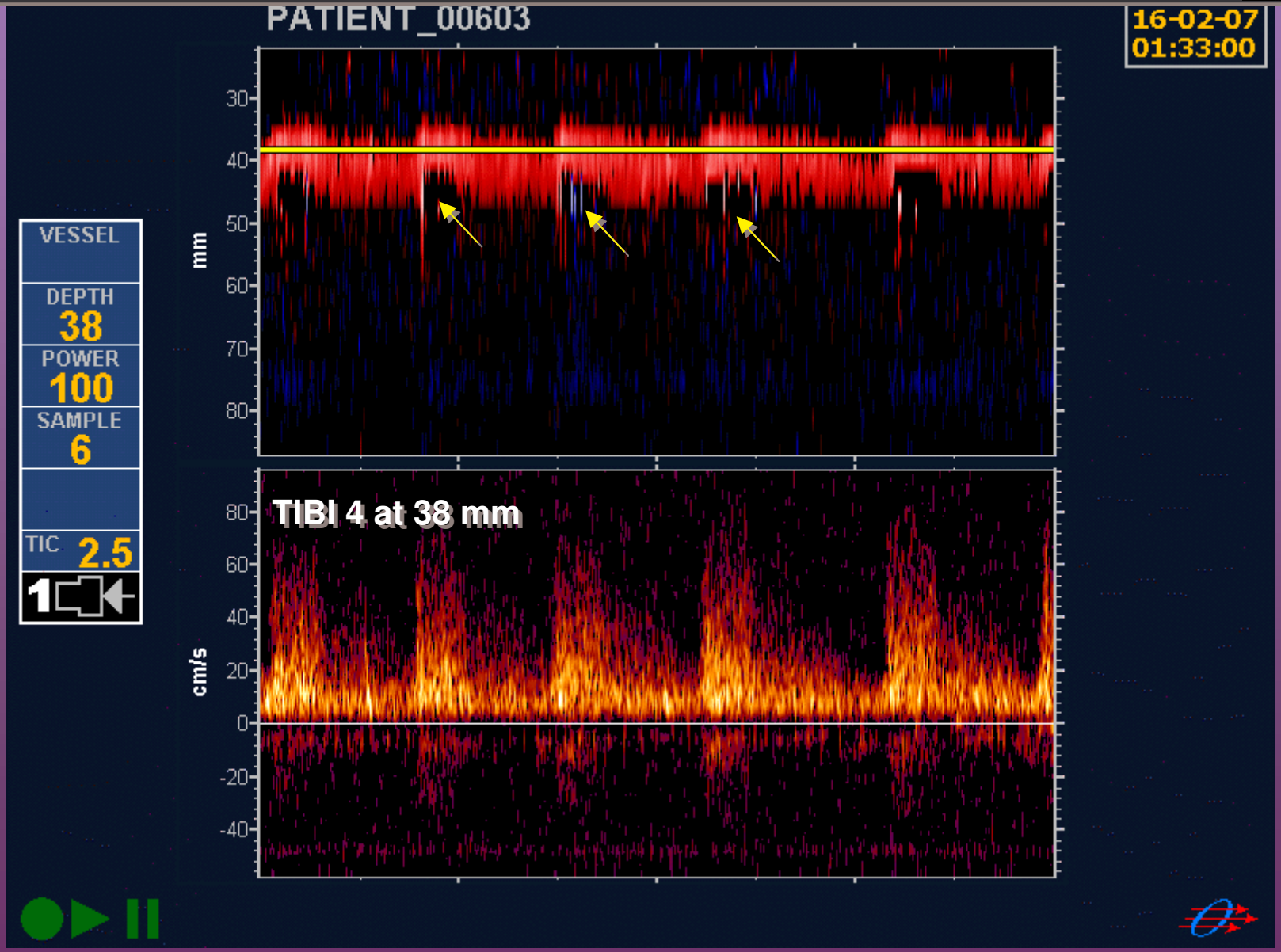




LMCA occlusion
NIHSS score 5

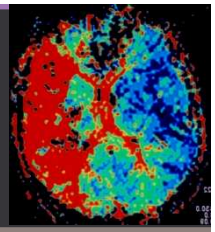
TIBI 4 at 38 mm
Time: 8 min 22 sec

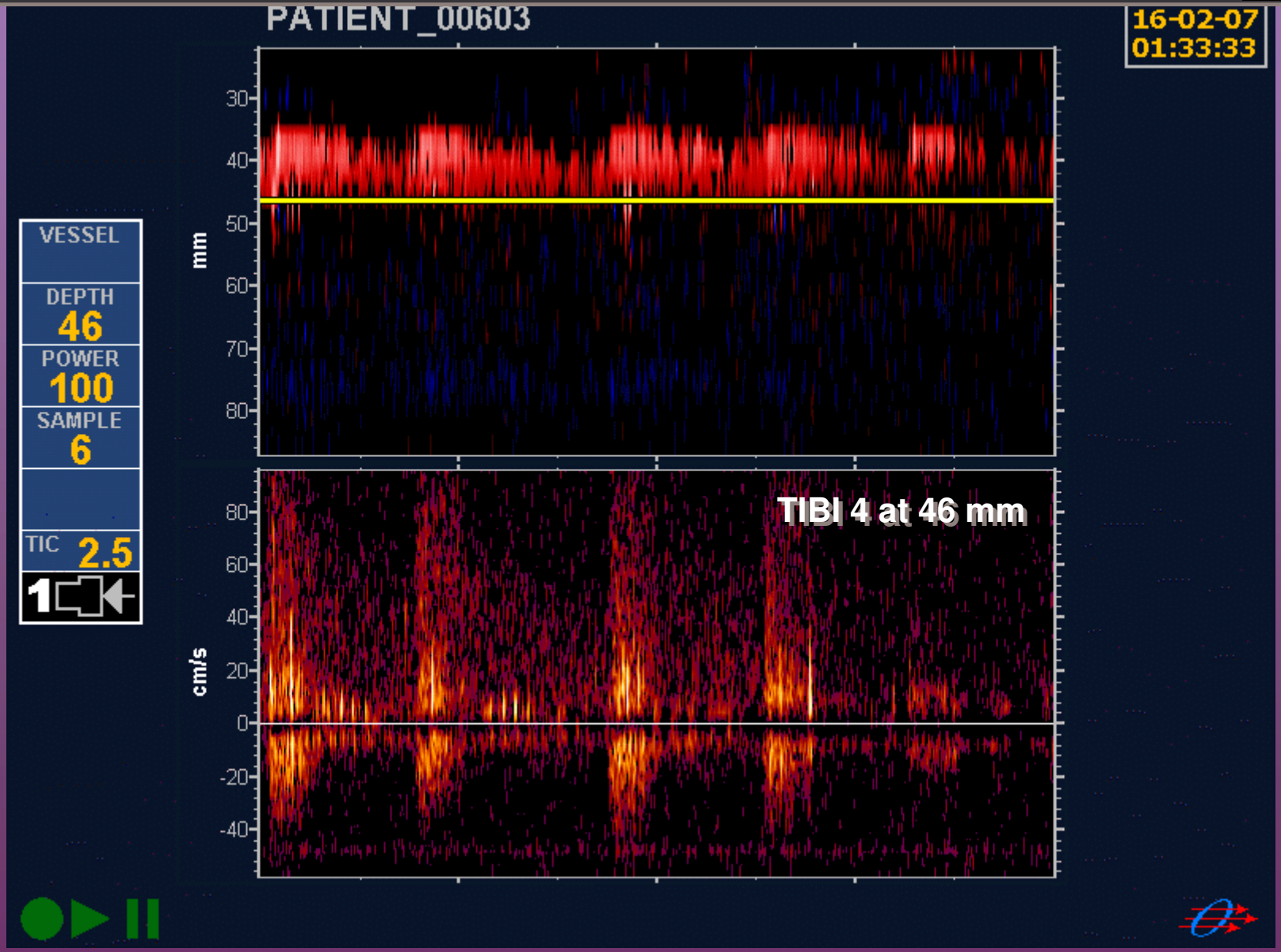




LMCA occlusion
NIHSS score 5

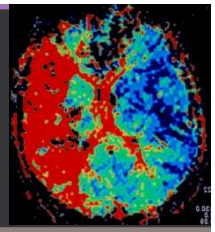
TIBI 4 at 46 mm
Time: 8 min 51 sec

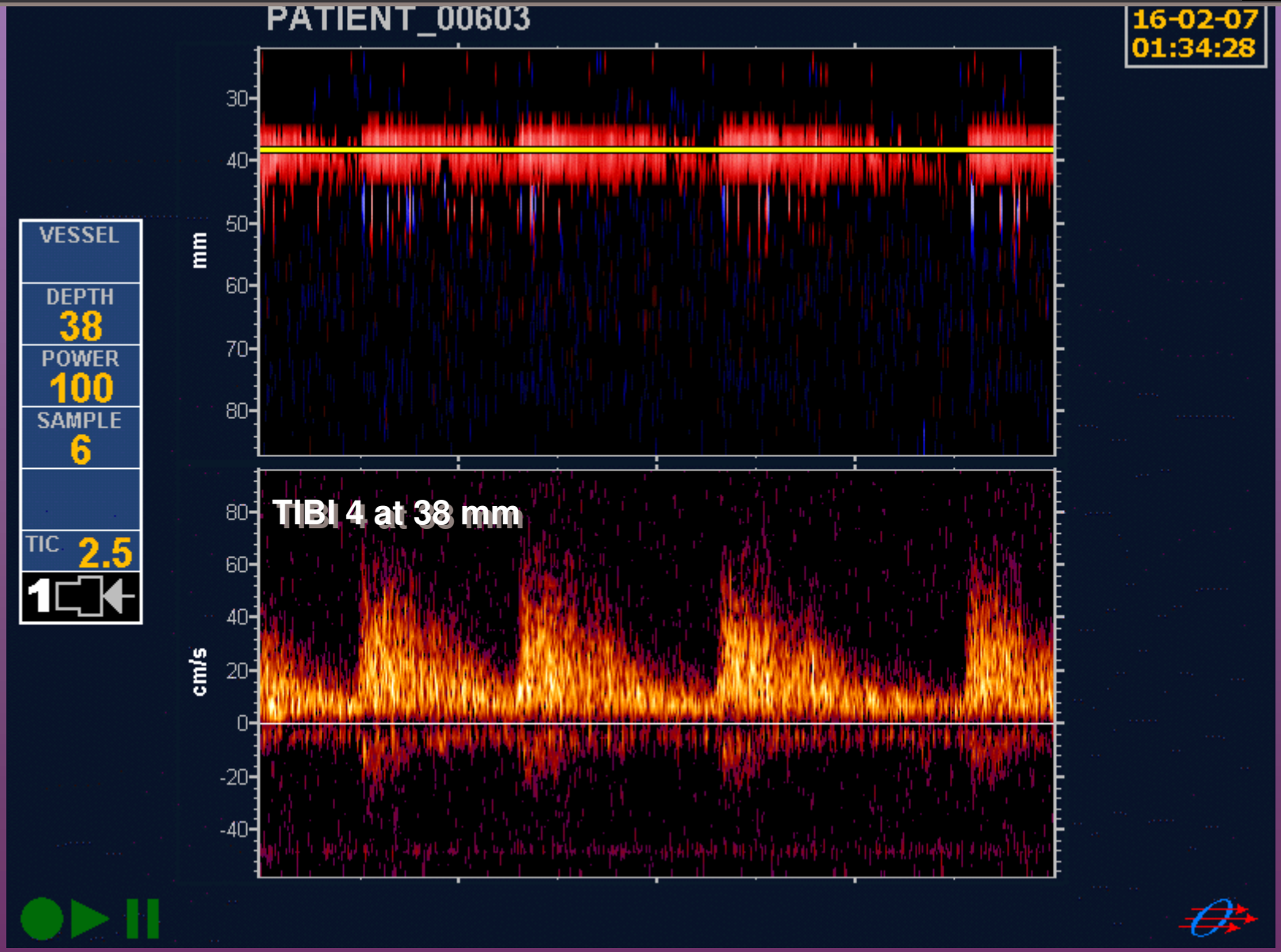




LMCA occlusion
NIHSS score 5

TIBI 4 at 38 mm
Time: 9 min 28 sec

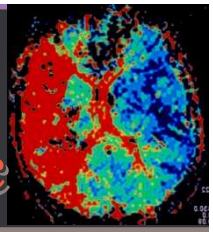


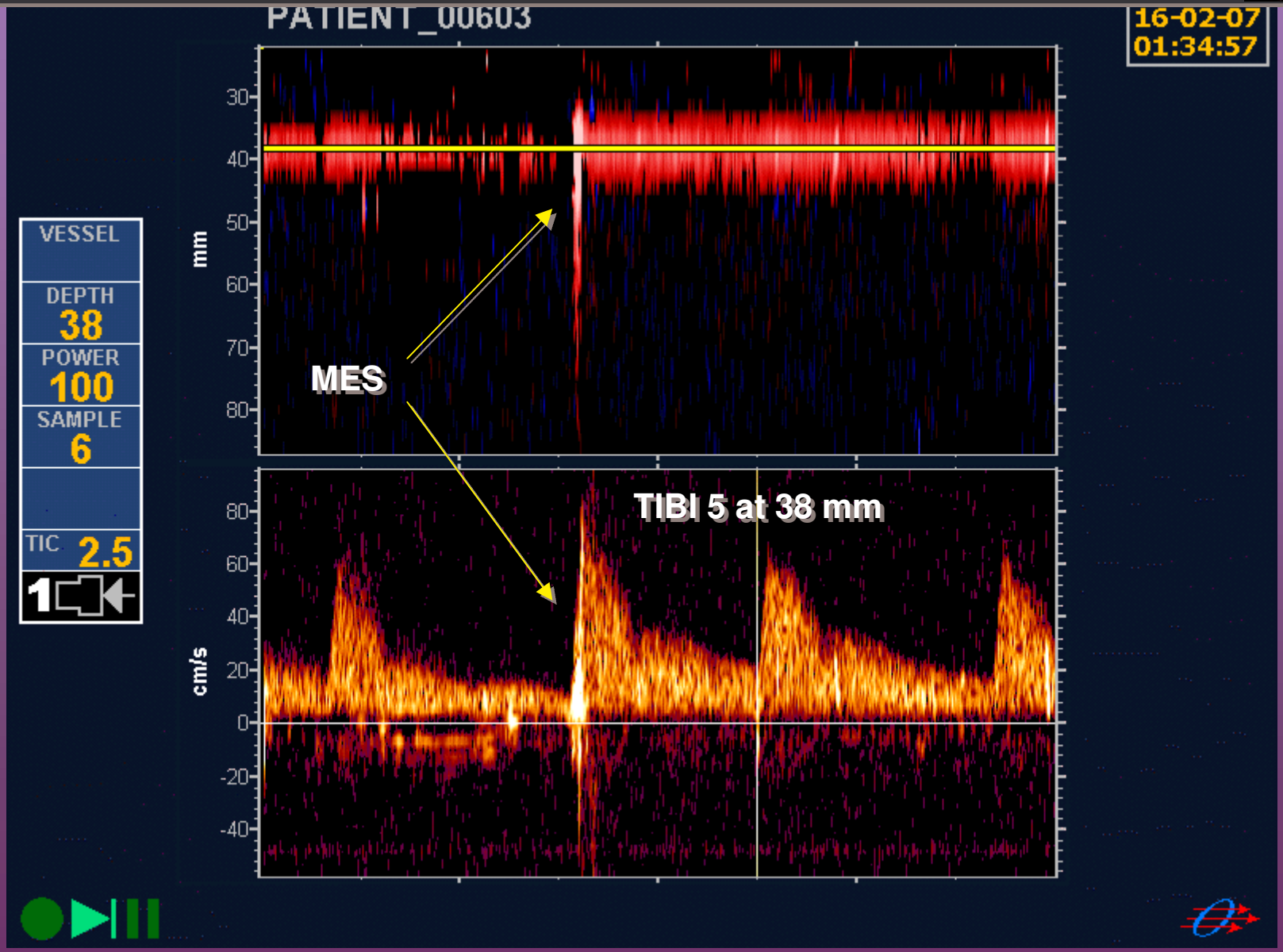


Complete Left MCA recanalization

NIHSS score 1

Time: 10 min 18 sec

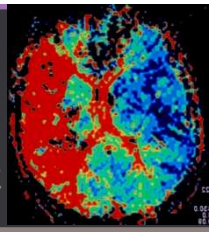


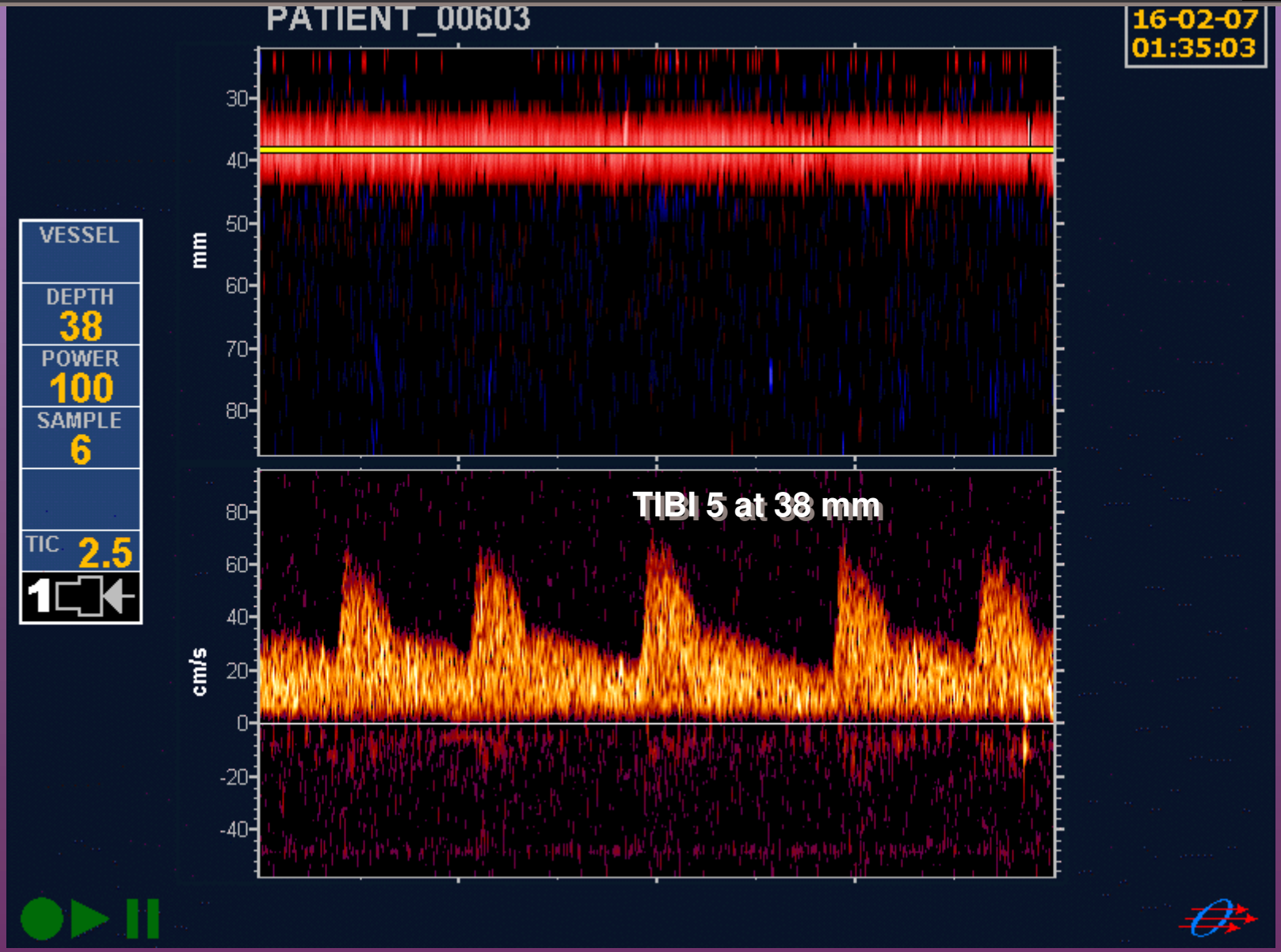


Complete Left MCA recanalization

NIHSS score 1

Time: 11 min 12 sec

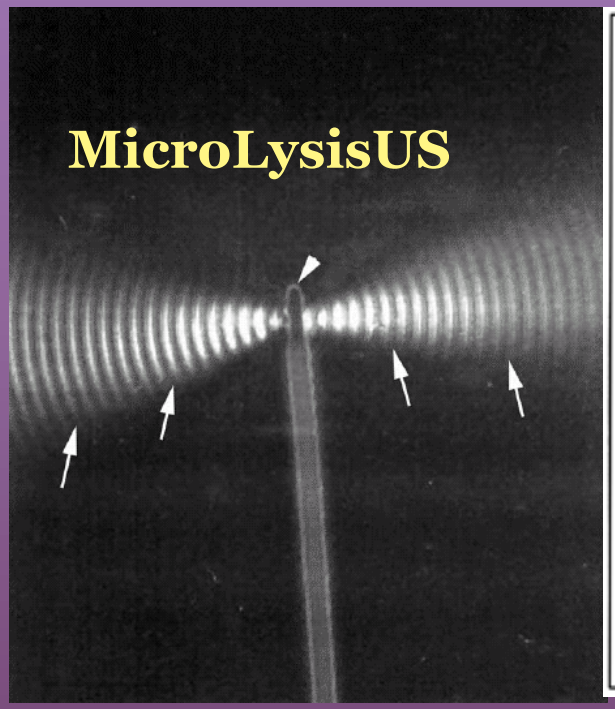


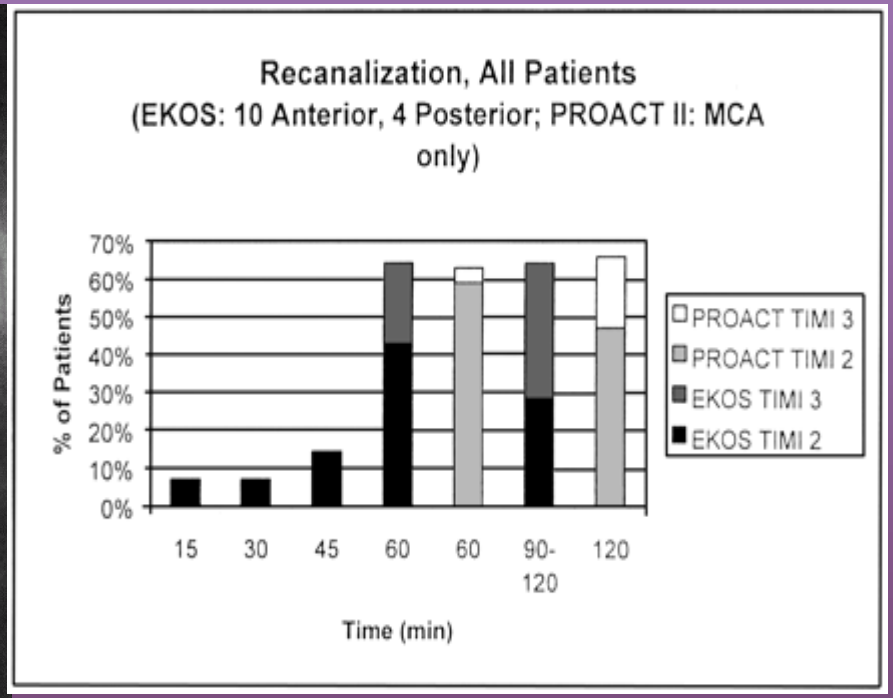


TUCSON TRIAL
Transcranial Ultrasound in Clinical SONolysis

A Phase 1-2, Randomized, Placebo Controlled, Open-Label, Dose Escalation Study to Evaluate the Safety, Tolerability, and Activity of Ascending Single Doses of MRX-801 with Continuous Ultrasound Administration in subjects with Acute Ischemic Stroke Receiving Treatment with Intravenous Tissue Plasminogen Activator.

EKOS
MicroLysUS





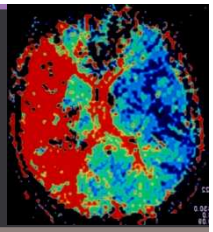
Stroke 3-6h.+ IA tPA.

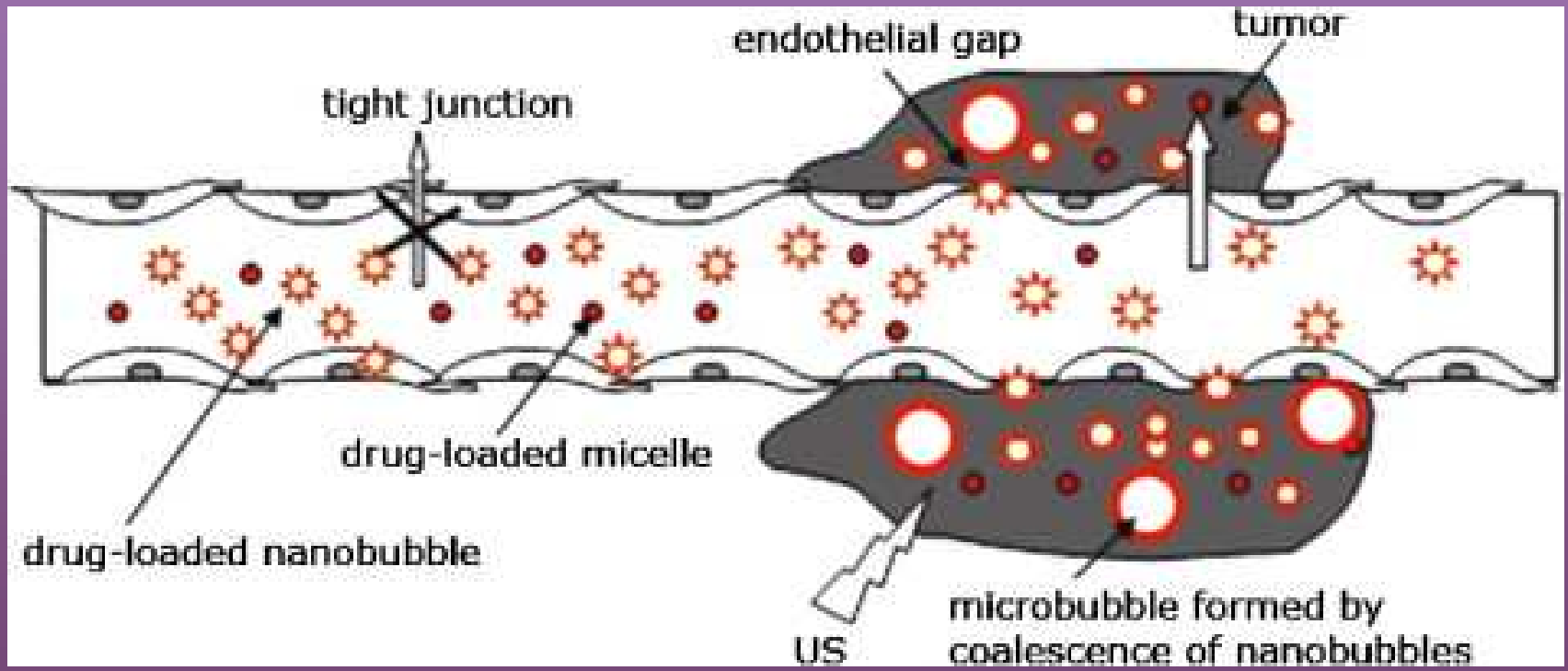
Endovascular lysis with US (EKOS)

Increase of the surface of thrombus exposed to tPA.

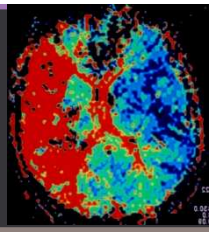
AJNR 24:534–538,2003

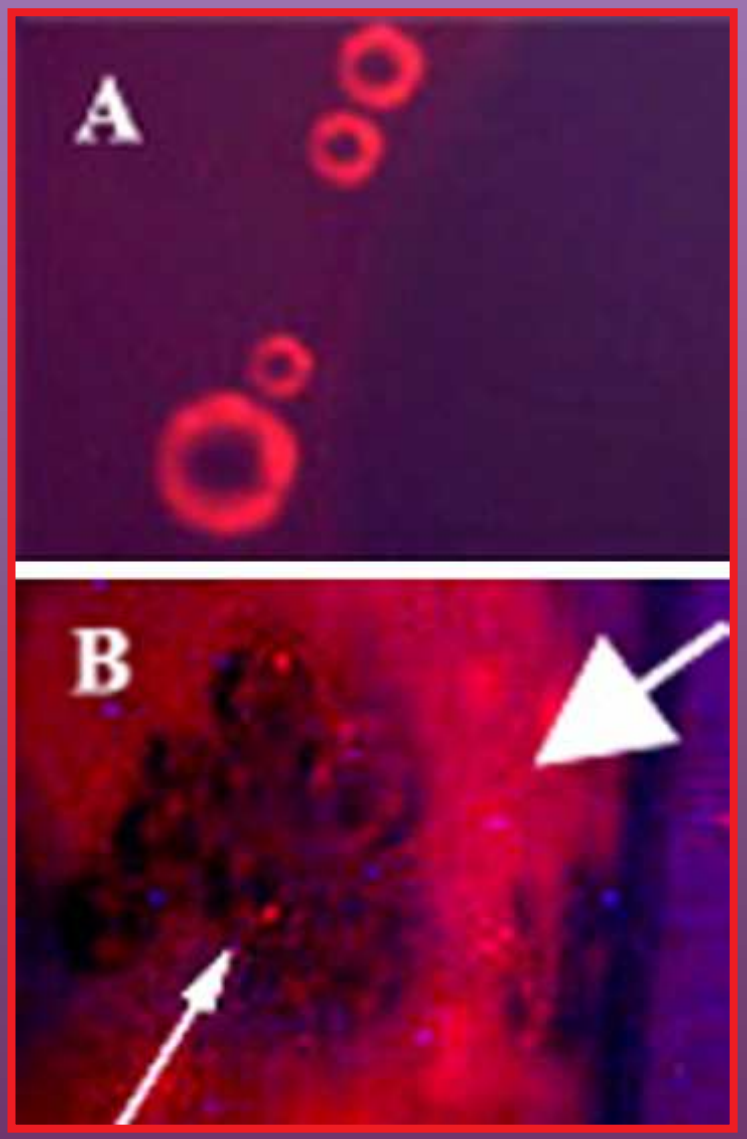
Loaded-microbubbles

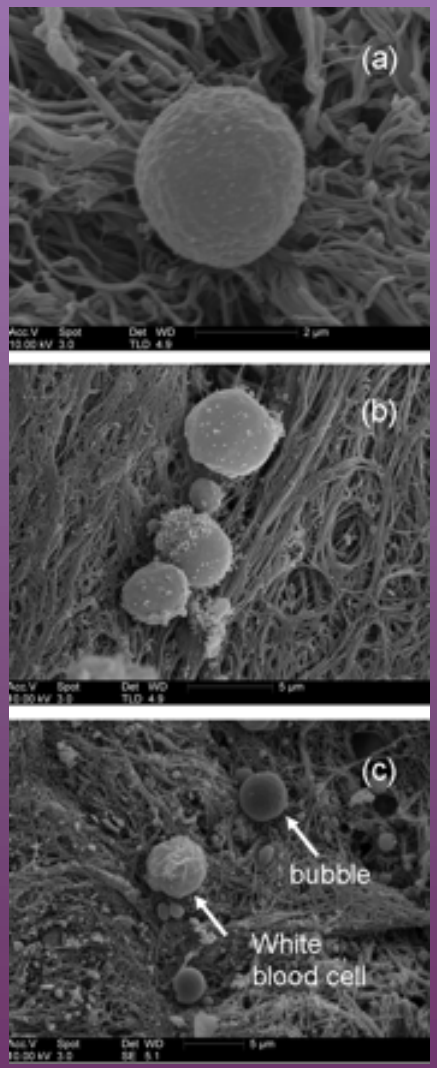




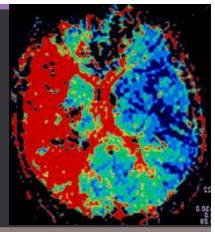
targeted-microbubbles







Conclusions



Diagnostic (2MHz) US accelerates thrombolysis with tPA and TNK in acute stroke

MB induces further acceleration of US-enhanced thrombolysis

-Faster and more complete recanalization

-Trend to better short-term clinical outcome

A multicenter trial of MB-enhanced sonothrombolysis to verify these results is necessary